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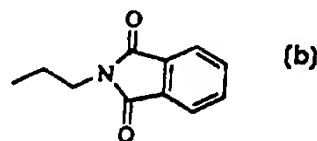
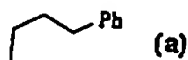
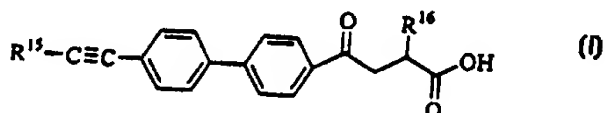
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(54) Title: INHIBITION OF MATRIX METALLOPROTEASES BY ACETYLENE CONTAINING COMPOUNDS

(57) Abstract

Matrix metalloprotease inhibiting compounds, pharmaceutical compositions thereof and a method of disease treatment using such compounds are presented. The compounds of the invention have the generalized formula (I) where R¹⁵ is selected from the group comprising: HOCH₂, MeOCH₂, (n-Pr)₂NCH₂, CH₃CO₂CH₂, EtOCO₂CH₂, HO(CH₂)₂, CH₃CO₂(CH₂)₂, HO₂C(CH₂)₂, OHC(CH₂)₂, HO(CH₂)₄, Ph, 3-HO-Ph, and PhCH₂OCH₂; and R¹⁶ is (a) or (b). These compounds are useful for inhibiting matrix metalloproteases and, therefore, combating conditions to which MMP's contribute, such as osteoarthritis, rheumatoid arthritis, septic arthritis, periodontal disease, corneal ulceration, proteinuria, aneurysmal aortic disease, dystrophic epidermolysis, bullosa, conditions leading to inflammatory responses, osteopenias mediated by MMP activity, temporo mandibular joint disease, demyelating diseases of the nervous system, tumor metastasis or degenerative cartilage loss following traumatic joint injury, and coronary thrombosis from atherosclerotic plate rupture. The present invention also provides pharmaceutical compositions and methods for treating such conditions.



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Title: Inhibition of Matrix Metalloproteases by acetylene containing compounds

BACKGROUND OF THE INVENTION

Field of the Invention

5 This invention relates to enzyme inhibitors, and more particularly, to novel biaryl acetylene containing compounds or derivatives thereof useful for inhibiting matrix metalloproteases.

Description of the Related Art

10 The matrix metalloproteases (a.k.a. matrix metalloendo-proteinases or MMPs) are a family of zinc endoproteinases which include, but are not limited to, interstitial collagenase (a.k.a. MMP-1), stromelysin (a.k.a., proteoglycanase, transin, or MMP-3), gelatinase A (a.k.a. 72kDa-gelatinase or MMP-2) and gelatinase B (a.k.a., 95kDa-gelatinase or MMP-9). These MMPs are secreted by a variety of cells including fibroblasts and chondrocytes, along with natural proteinaceous inhibitors known as TIMPs (Tissue Inhibitor of MetalloProteinase).

15 All of these MMPs are capable of destroying a variety of connective tissue components of articular cartilage or basement membranes. Each MMP is secreted as an inactive proenzyme which must be cleaved in a subsequent step before it is able to exert its own proteolytic activity. In addition to the matrix destroying effect, certain of these MMPs such as MMP-3 have been implemented as the *in vivo* activator for other MMPs such as MMP-1 and MMP-9 (Ito, et al., Arch Biochem Biophys. 267, 211, 1988; Ogata, et al., J. Biol. Chem. 267, 3581, 1992). Thus, a cascade
20 of proteolytic activity can be initiated by an excess of MMP-3. It follows that specific MMP-3 inhibitors should limit the activity of other MMPs that are not directly inhibited by such inhibitors.

It has also been reported that MMP-3 can cleave and thereby inactivate the endogenous inhibitors of other proteinases such as elastase (Winyard, et al., FEBS Letts. 279, 1, 91, 1991).

Inhibitors of MMP-3 could thus influence the activity of other destructive proteinases by modifying the level of their endogenous inhibitors.

A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease activity or by an imbalance in the ratio of the MMPs to the TIMPs. These include:

5 a) osteoarthritis (Woessner, et al., *J. Biol.Chem.* 259(6), 3633, 1984; Phadke, et al., *J. Rheumatol.* 10, 852, 1983), b) rheumatoid arthritis (Mullins, et al., *Biochim. Biophys. Acta* 695, 117, 1983; Woolley, et al., *Arthritis Rheum.* 20, 1231, 1977; Gravalles, et al., *Arthritis Rheum.* 34, 1076, 1991), c) septic arthritis (Williams, et al., *Arthritis Rheum.* 33, 533, 1990), d) tumor metastasis (Reich, et al., *Cancer Res.* 48, 3307, 1988, and Matrisian, et al., *Proc. Nat'l. Acad. Sci., USA* 83, 9413, 1986), e) periodontal diseases (Overall, et al., *J. Periodontal Res.* 22, 81, 1987), f) corneal ulceration (Burns, et al., *Invest. Ophthalmol. Vis. Sci.* 30, 1569, 1989), g) proteinuria (Baricos, et al., *Biochem. J.* 254, 609, 1988), h) coronary thrombosis from atherosclerotic plaque rupture (Henney, et al., *Proc. Nat'l. Acad. Sci., USA* 88, 8154-8158, 1991), i) aneurysmal aortic disease (Vine, et al., *Clin. Sci.* 81, 233, 1991), j) birth control (Woessner, et al., *Steroids* 54, 491, 1989), k) dystrophic epidermolysis bullosa (Kronberger, et al., *J. Invest. Dermatol.* 79, 208, 1982), and l) degenerative cartilage loss following traumatic joint injury, m) conditions leading to inflammatory responses, osteopenias mediated by MMP activity, n) temporomandibular joint disease, o) demyelinating diseases of the nervous system (Chantry, et al., *J. Neurochem.* 50, 688, 1988).

20 The need for new therapies is especially important in the case of arthritic diseases. The primary disabling effect of osteoarthritis (OA), rheumatoid arthritis (RA) and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal anti-

inflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. MMP inhibitors are expected to halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

5 Proteases are critical elements at several stages in the progression of metastatic cancer. In this process, the proteolytic degradation of structural protein in the basal membrane allows for expansion of a tumor in the primary site, evasion from this site as well as homing and invasion in distant, secondary sites. Also, tumor induced angiogenesis is required for tumor growth and is dependent on proteolytic tissue remodeling. Transfection experiments with various types of
10 proteases have shown that the matrix metalloproteases play a dominant role in these processes in particular gelatinases A and B (MMP-2 and MMP-9, respectively). For an overview of this field see Mullins, et al., *Biochim. Biophys. Acta* 695, 177, 1983; Ray, et al., *Eur. Respir. J.* 7, 2062, 1994; Birkedal-Hansen, et al., *Crit. Rev. Oral Biol. Med.* 4, 197, 1993.

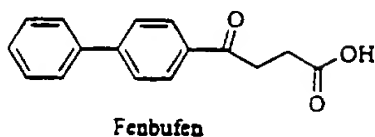
 Furthermore, it was demonstrated that inhibition of degradation of extracellular matrix by
15 the native matrix metalloprotease inhibitor TIMP-2 (a protein) arrests cancer growth (DeClerck, et al., *Cancer Res.* 52, 701, 1992) and that TIMP-2 inhibits tumor-induced angiogenesis in experimental systems (Moses, et al. *Science* 248, 1408, 1990). For a review, see DeClerck, et al., *Ann. N. Y. Acad. Sci.* 732, 222, 1994. It was further demonstrated that the synthetic matrix metalloprotease inhibitor batimastat when given intraperitoneally inhibits human colon tumor
20 growth and spread in an orthotopic model in nude mice (Wang, et al. *Cancer Res.* 54, 4726, 1994) and prolongs the survival of mice bearing human ovarian carcinoma xenografts (Davies, et. al.,

Cancer Res. 53, 2087, 1993). The use of this and related compounds has been described in Brown, et al., WO-9321942 A2.

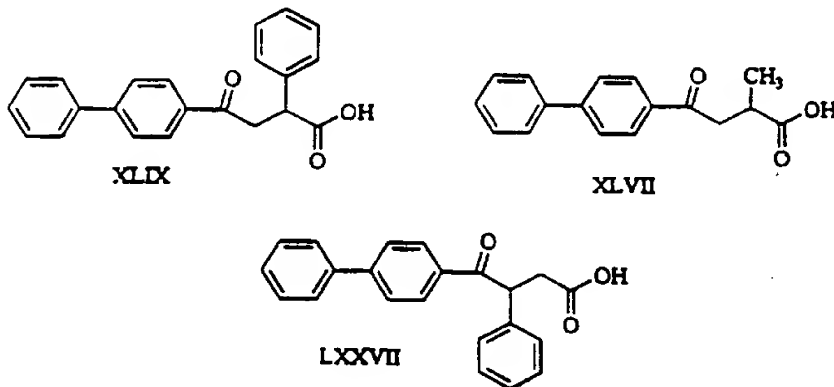
There are several patents and patent applications claiming the use of metalloproteinase inhibitors for the retardation of metastatic cancer, promoting tumor regression, inhibiting cancer cell proliferation, slowing or preventing cartilage loss associated with osteoarthritis or for treatment of other diseases as noted above (e.g. Levy, et al., WO-9519965 A1; Beckett, et al., WO-9519956 A1; Beckett, et al., WO-9519957 A1; Beckett, et al., WO-9519961 A1; Brown, et al., WO-9321942 A2; Crimmin, et al., WO-9421625 A1; Dickens, et al., U.S. Pat. No. 4,599,361; Hughes, et al., U.S. Pat. No. 5,190,937; Broadhurst, et al., EP 574758 A1; Broadhurst, et al., EP 276436; and Myers, et al., EP 520573 A1. The preferred compounds of these patents have peptide backbones with a zinc complexing group (hydroxamic acid, thiol, carboxylic acid or phosphinic acid) at one end and a variety of sidechains, both those found in the natural amino acids as well as those with more novel functional groups. Such small peptides are often poorly absorbed, exhibiting low oral bioavailability. They are also subject to rapid proteolytic metabolism, thus having short half lives. As an example, batimastat, the compound described in Brown, et al., WO-9321942 A2, can only be given intra peritoneally.

Certain 3-biphenoylpropanoic and 4-biaryloylbutanoic acids are described in the literature as anti-inflammatory, anti-platelet aggregation, anti-phlogistic, anti-proliferative, hypolipidemic, antirheumatic, analgesic, and hypocholesterolemic agents. In none of these examples is a reference made to MMP inhibition as a mechanism for the claimed therapeutic effect. Certain related compounds are also used as intermediates in the preparation of liquid crystals.

Specifically, Tomcufcik, et al., US patent 3,784,701 claims certain substituted benzoylpropionic acids to treat inflammation and pain. These compounds include 3-biphenoylpropionic acid (a.k.a. fenbufen) shown below.

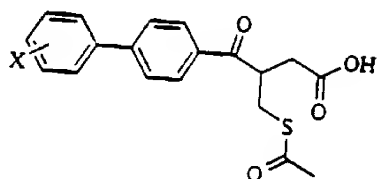


Child, et al., J. Pharm. Sci. 66, 466, 1977 describes structure-activity relationships of several analogs of fenbufen. These include several compounds in which the biphenyl ring system is substituted or the propanoic acid portion is substituted with phenyl, halogen, hydroxyl or methyl, or the carboxylic acid or carbonyl functions are converted to a variety of derivatives. No compounds are described which contain a 4'-substituted biphenyl and a substituted propanoic acid portion combined in one molecule. The phenyl (compounds XLIX and LXXVII) and methyl (compound XLVII) substituted compounds shown below were described as inactive.



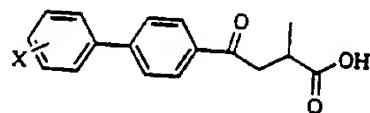
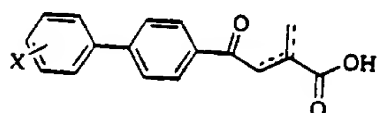
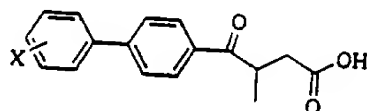
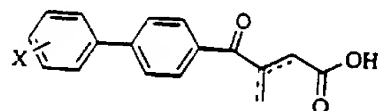
Kameo, et al., Chem. Pharm. Bull. 36, 2050, 1988 and Tomizawa, et al., JP patent 62132825 A2 describe certain substituted 3-biphenoylpropionic acid derivatives and analogs thereof including

the following. Various compounds with other substituents on the propionic acid portion are described, but they do not contain biphenyl residues.



wherein X = H, 4'-Br, 4'-Cl, 4'-CH₃, or 2'-Br.

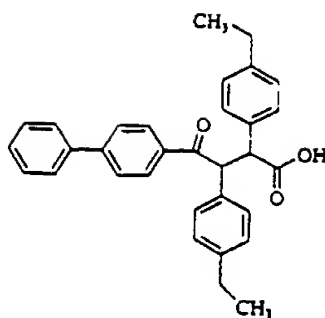
Cousse, et al., Eur. J. Med. Chem. 22, 45, 1987 describe the following methyl and methylene substituted 3-biphenoyl-propanoic and -propenoic acids. The corresponding compounds in which the carbonyl is replaced with either CH₂OH or CH₃ are also described.



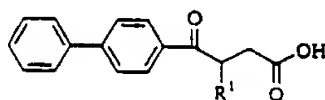
wherein X = H, Cl, Br, CH₃O, F, or NH₂.

Nichl, et al. DE patent 1957750 also describes certain of the above methylene substituted biphenoylpropanoic acids.

El-Hashash, et al., Revue Roum. Chim. 23, 1581, 1978 describe products derived from β -aroyl-acrylic acid epoxides including the following biphenyl compound. No compounds substituted on the biphenyl portion are described.

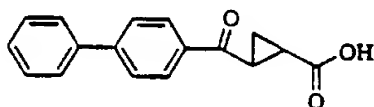


Kitamura, et al., JP patent 60209539 describes certain biphenyl compounds used as intermediates for the production of liquid crystals including the following. The biphenyl is not substituted in these intermediates.

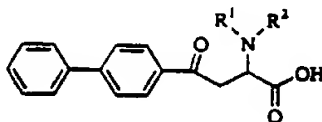


wherein R¹ is an alkyl of 1-10 carbons.

Thyes, et al., DE patent 2854475 uses the following compound as an intermediate. The biphenyl group is not substituted.

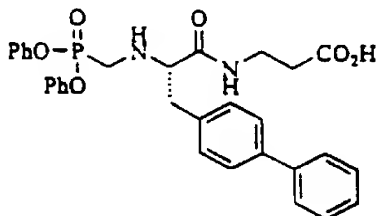


Sammour, et al., *Egypt J. Chem.* **15**, 311, 1972 and Couquelet, et al., *Bull. Soc. Chim. Fr.* **2**, 3196, 1971 describe certain dialkylamino substituted biphenylpropanoic acids including the following. In no case is the biphenyl group substituted.

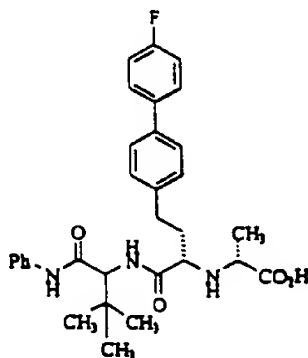


wherein R¹, R² = alkyl, benzyl, H, or, together with the nitrogen, morpholinyl.

Others have disclosed a series of biphenyl-containing carboxylic acids, illustrated by the compound shown below, which inhibit neural endopeptidase (NEP 24.11), a membrane-bound zinc metalloprotease (Stanton, et al., Bioorg. Med. Chem. Lett. 4, 539, 1994; Lombaert, et al., Bioorg. Med. Chem. Lett. 4, 2715, 1994; Lombaert, et al., Bioorg. Med. Chem. Lett. 5, 145, 1995; Lombaert, et al., Bioorg. Med. Chem. Lett. 5, 151, 1995).



It has been reported that N-carboxyalkyl derivatives containing a biphenylethylglycine, illustrated by the compound shown below, are inhibitors of stromelysin-1 (MMP-3), 72 kDA gelatinase (MMP-2) and collagenase (Durette, et al., WO-9529689).



It would be desirable to have effective MMP inhibitors which possess improved bioavailability and biological stability relative to the peptide-based compounds of the prior art, and

which can be optimized for use against particular target MMPs. Such compounds are the subject of the present application.

The development of efficacious MMP inhibitors would afford new therapies for diseases mediated by the presence of, or an excess of MMP activity, including osteoarthritis, rheumatoid arthritis, septic arthritis, tumor metastasis, periodontal diseases, corneal ulcerations, and proteinuria. Several inhibitors of MMPs have been described in the literature, including thiols (Beszant, et al., J. Med. Chem. 36, 4030, 1993), hydroxamic acids (Wahl, et al. Bioorg. Med. Chem. Lett. 5, 349, 1995; Conway, et al. J. Exp. Med. 182, 449, 1995; Porter, et al., Bioorg. Med. Chem. Lett. 4, 2741, 1994; Tomczuk, et al., Bioorg. Med. Chem. Lett. 5, 343, 1995; Castelhana, et al., Bioorg. Med. Chem. Lett. 5, 1415, 1995), phosphorous-based acids (Bird, et al. J. Med. Chem. 37, 158, 1994; Morphy, et al., Bioorg. Med. Chem. Lett. 4, 2747, 1994; Kortylewicz, et al., J. Med. Chem. 33, 263, 1990), and carboxylic acids (Chapman, et al. J. Med. Chem. 36, 4293, 1993; Brown, et al., J. Med. Chem. 37, 674, 1994; Morphy, et al., Bioorg. Med. Chem. Lett. 4, 2747, 1994; Stack, et al., Arch. Biochem. Biophys. 287, 240, 1991; Ye, et al., J. Med. Chem. 37, 206, 1994; Grobelny, et al., Biochemistry 24, 6145, 1985; Mookhtiar, et al., Biochemistry 27, 4299, 1988). However, these inhibitors generally contain peptidic backbones, and thus usually exhibit low oral bioactivity due to poor absorption and short half lives due to rapid proteolysis. Therefore, there remains a need for improved MMP inhibitors.

SUMMARY OF THE INVENTION

This invention provides compounds having matrix metalloprotease inhibitory activity. These compounds are useful for inhibiting matrix metalloproteases and, therefore, combating conditions

to which MMP's contribute. Accordingly, the present invention also provides pharmaceutical compositions and methods for treating such conditions.

The compounds described relate to a method of treating a mammal comprising administering to the mammal a matrix metalloprotease inhibiting amount of a compound according to the invention sufficient to:

- (a) alleviate the effects of osteoarthritis, rheumatoid arthritis, septic arthritis, periodontal disease, corneal ulceration, proteinuria, aneurysmal aortic disease, dystrophic epidermolysis bullosa, conditions leading to inflammatory responses, osteopenias mediated by MMP activity, temporomandibular joint disease, demyelating diseases of the nervous system;
- (b) retard tumor metastasis or degenerative cartilage loss following traumatic joint injury;
- (c) reduce coronary thrombosis from atherosclerotic plaque rupture; or
- (d) effect birth control

The compounds of the present invention are also useful scientific research tools for studying functions and mechanisms of action of matrix metalloproteases in both *in vivo* and *in vitro* systems. Because of their MMP-inhibiting activity, the present compounds can be used to modulate MMP action, thereby allowing the researcher to observe the effects of reduced MMP activity in the experimental biological system under study.

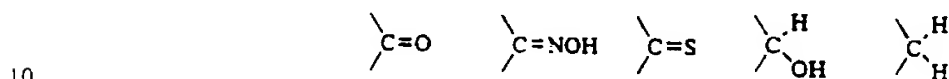
This invention relates to compounds having matrix metalloprotease inhibitory activity and the generalized formula:



In the above generalized formula (L), T₁A represents a substituted or unsubstituted aromatic 6-membered ring or heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms independently selected from the group of N, O, or S. T represents a substituted acetylenic moiety.

In the generalized formula (L), B represents an aromatic 6-membered ring or a heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms independently selected from the group of N, O, or S. It is referred to as the B ring or B unit. When N is employed in conjunction with either S or O in the B ring, these heteroatoms are separated by at least one carbon atom.

In the generalized formula (L), D represents



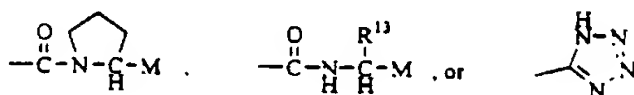
In the generalized formula (L), E represents a chain of n carbon atoms bearing m substituents R⁶ in which the R⁶ groups are independent substituents, or constitute spiro or nonspiro rings. Rings may be formed in two ways: a) two groups R⁶ are joined, and taken together with the chain atom(s) to which the two R⁶ group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R⁶ is joined to the chain on which this one group R⁶ resides, and taken together with the chain atom(s) to which the R⁶ group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 or 3, and the number m of R⁶ substituents is an integer of 1 - 3. The number of carbons in the totality of R⁶ groups is at least two.

20 Each group R⁶ is alkyl, alkenyl, alkynyl, heteroaryl, non-aromatic cyclic, and combinations thereof optionally substituted with one or more heteroatoms as described more fully below. In the

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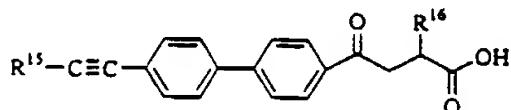
generalized formula (L). E is a substituted mono- or bicyclic moiety optionally substituted with one or more heteroatoms.

In the generalized formula (L), G represents $-\text{PO}_3\text{H}_2$, $-\text{M}$,

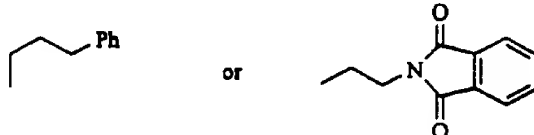


in which M represents $-\text{CO}_2\text{H}$, $-\text{CON}(\text{R}^{11})_2$ or $-\text{CO}_2\text{R}^{12}$, and R^{13} represents any of the side chains of the 19 noncyclic naturally occurring amino acids.

The most preferred compounds of the invention are:



where R^{15} is selected from the group comprising: HOCH_2 , MeOCH_2 , $(n\text{-Pr})_2\text{NCH}_2$, $\text{CH}_3\text{CO}_2\text{CH}_2$, $\text{EtOCO}_2\text{CH}_2$, $\text{HO}(\text{CH}_2)_2$, $\text{CH}_3\text{CO}_2(\text{CH}_2)_2$, $\text{HO}_2\text{C}(\text{CH}_2)_2$, $\text{OHC}(\text{CH}_2)_2$, $\text{HO}(\text{CH}_2)_3$, Ph, 3-HO-Ph, and $\text{PhCH}_2\text{OCH}_2$; and R^{16} is



Pharmaceutically acceptable salts of these compounds are also within the scope of the invention.

In most related reference compounds of the prior art, the biphenyl portion of the molecule is unsubstituted, and the propanoic or butanoic acid portion is either unsubstituted or has a single methyl or phenyl group. Presence of the larger phenyl group has been reported to cause prior art compounds to be inactive as anti-inflammatory analgesic agents. See, for example, Child, et al., J.

Pharm. Sci. 66, 466 (1977). By contrast, it has now been found that compounds which exhibit potent MMP inhibitory activity contain a substituent of significant size on the propanoic or butanoic portion of the molecule. The biphenyl portions of the best MMP inhibitors also preferably contain a substituent on the 4' position, although when the propanoic or butanoic portions are optimally substituted, the unsubstituted biphenyl compounds of the invention have sufficient activity to be considered realistic drug candidates.

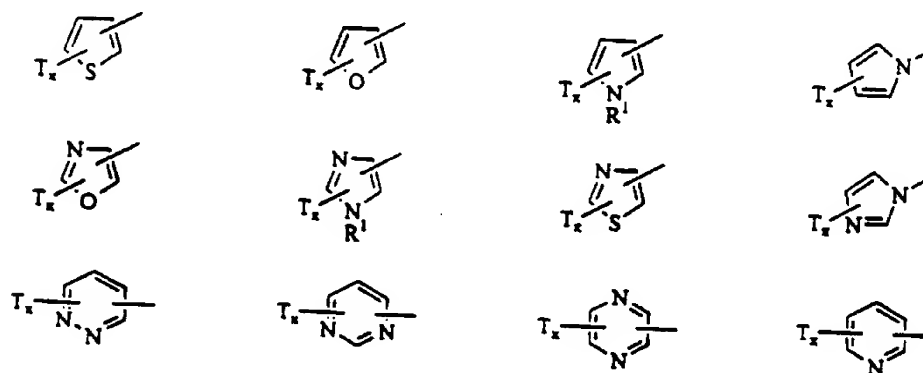
The foregoing merely summarizes certain aspects of the present invention and is not intended, nor should it be construed, to limit the invention in any way. All of the patents and other publications recited in this specification are hereby incorporated by reference in their entirety.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

More particularly, the compounds of the present invention are materials having matrix metalloprotease inhibitory activity and the generalized formula:



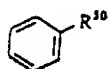
in which T_A represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



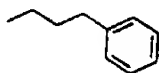


in which R^1 represents H or alkyl of 1 - 3 carbons.

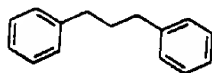
Throughout this application, in the displayed chemical structures, an open bond indicates the point at which the structure joins to another group. For example,



where R^{10} is



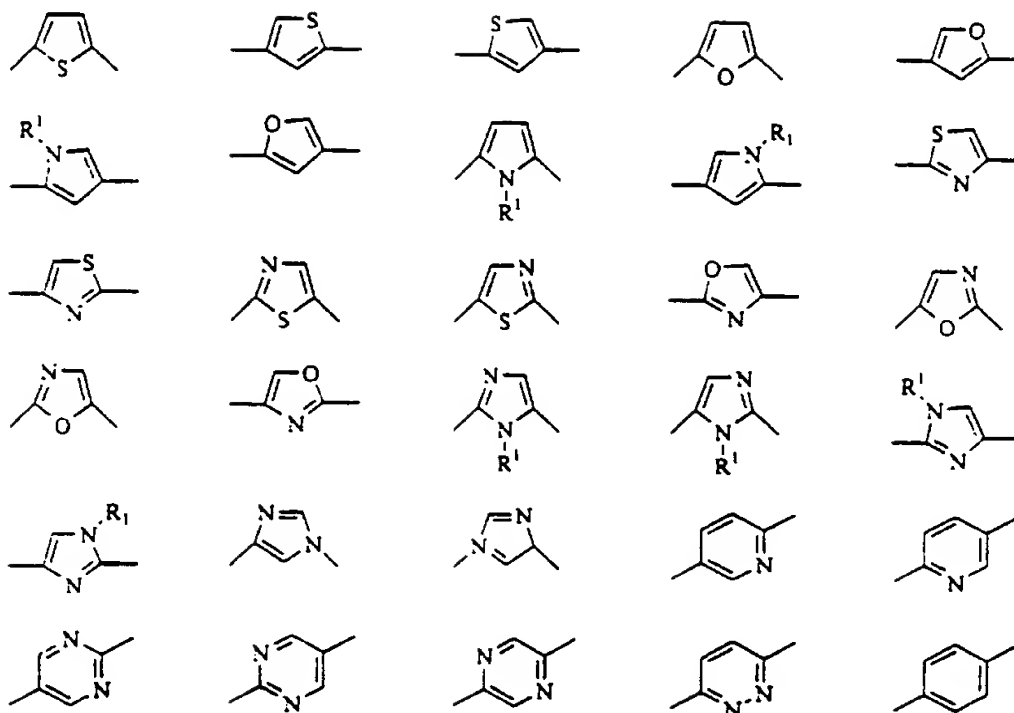
is the structure



In these structures, the aromatic ring is referred to as the A ring or A unit, and T represents a substituent group, referred to as a T group or T unit. T is a substituted acetylenic moiety and x is 1.

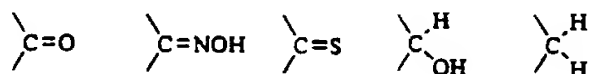
The B ring of generalized formula (L) is a substituted or unsubstituted aromatic or heteroaromatic ring, in which any substituents are groups which do not cause the molecule to fail to fit the active site of the target enzyme, or disrupt the relative conformations of the A and B rings, such that they would be detrimental. Such substituents may be moieties such as lower alkyl, lower alkoxy, CN, NO₂, halogen, etc., but are not to be limited to such groups.

In the generalized formula (L), B represents an aromatic or heteroaromatic ring selected from the group consisting of:



in which R^1 is defined as above. These rings are referred to as the B ring or B unit.

In the generalized formula (L), D represents the moieties:



In the generalized formula (L), E represents a chain of n carbon atoms bearing m substituents R^6 , referred to as R^6 groups or R^6 units. The R^6 groups are independent substituents, or constitute spiro or nonspiro rings. Rings may be formed in two ways: a) two groups R^6 are joined, and taken together with the chain atom(s) to which the two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which this one group R^6 resides, and taken together with the chain atom(s) to which the R^6 group is attached, and

any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 or 3, and the number m of R⁶ substituents is an integer of 1 - 3. The number of carbons in the totality of R⁶ groups is at least two.

Each group R⁶ is independently selected from the group consisting of the substituents listed below as items 1) - 14).

1) alkyl of 1 - 10 carbons, provided that if the A unit is phenyl, the B unit is phenylene, m is 1, n is 2, and the alkyl group is located on the alpha carbon relative to the D unit, then x is 1 or 2;

2) aryl of 6 - 10 carbons, provided that if the A unit is phenyl, the B unit is phenylene, the aryl group is phenyl, n is 2, and m is 1 or 2, then x is 1 or 2;

3) heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

4) arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

5) heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;

6) alkenyl of 2 - 10 carbons;

7) aryl-alkenyl in which the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;

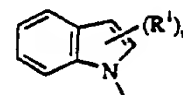
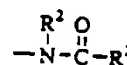
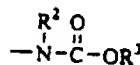
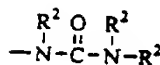
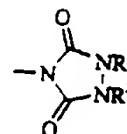
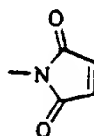
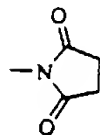
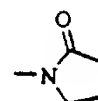
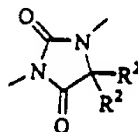
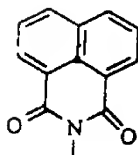
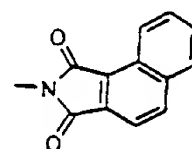
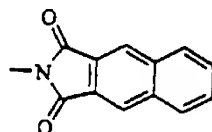
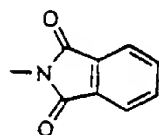
8) heteroaryl-alkenyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;

9) alkynyl of 2 - 10 carbons;

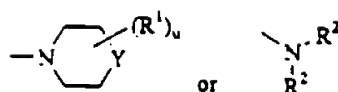
10) aryl-alkynyl in which the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;

11) heteroaryl-alkynyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;

12) $-(CH_2)_t R^7$ in which t is 0 or an integer of 1 - 5 and R^7 is selected from the group consisting of:



as well as corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom. In such R^7 groups, Y represents O or S; R^1 , R^2 , and R^3 are as defined above, and u is 0, 1, or 2 provided that when R^7 is



and the A unit is phenyl, the B unit is phenylene, m is 1, n is 2, and t is 0, then x is 1 or 2.

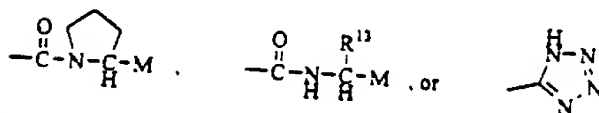
13)-(CH₂)_xZR⁸ in which v is an interger of 1 to 4, Z represents -S-, -S(O)-, -SO₂-, or
5 -O-, and R⁸ is selected from the group consisting of alkyl of 1 to 12 carbons, aryl of 6 to 10
carbons, heteroaryl comprising 4 to 9 carbons and at least one N, O, or S heteroatom;
arylalkyl in which the aryl portion contains 6 to 12 carbons and the alkyl portion contains
1 to 4 carbons; heteroarylalkyl in which the aryl portion contains 6 to 12 carbons and at least
one N, O, or S heteroatom and the alkyl portion contains 1 to 4 carbons; -C(O)R⁹ in which
10 the R⁹ represents alkyl of 2 to 6 carbons, aryl of 6 to 10 carbons, heteroaryl comprising 4 to
9 carbons and at least one N, O, or S heteroatom, and arylalkyl in which the aryl portion
contains 6 to 10 carbons or is a heteroaryl comprising 4 to 9 carbons and at least one N, O,
or S heteroatom, and the alkyl portion contains 1 to 4 carbons with the provisos that when
R⁸ is -C(O)R⁹, Z is -S- or -O-; when Z is -O-, R⁸ may also be -(C_qH_{2q}O)_rR³ in which q, r, and
15 R³ are as defined above; and when the A unit is phenyl, the B unit is phenylene, m is 1, n is
2, and v is 0, then x is 1 or 2; and

14)-(CH₂)_wSiR¹⁰, in which w is an integer of 1 to 3, and R¹⁰ represents alkyl of 1 to 2 carbons.

20 In addition, aryl or heteroaryl portions of any of the T or R⁶ groups optionally may bear up to two substituents selected from the group consisting of -(CH₂)_yC(R¹¹)(R¹²)OH, -(CH₂)_yOR¹¹, -(CH₂)_ySR¹¹, -(CH₂)_yS(O)R¹¹, -(CH₂)_yS(O)₂R¹¹, -(CH₂)_ySO₂N(R¹¹)₂, -(CH₂)_yN(R¹¹)₂, -(CH₂)_yN(R¹¹)COR¹², -OC(R¹¹)₂O- in which both oxygen atoms are connected to the aryl ring,

$-(CH_2)_yCOR^{11}$, $-(CH_2)_yCON(R^{11})_2$, $-(CH_2)_yCO_2R^{11}$, $-(CH_2)_yOCOR^{11}$, -halogen, -CHO, $-CF_3$, $-NO_2$, -CN, and $-R^{12}$, in which y is 0 - 4; R^{11} represents H or alkyl of 1 - 4 carbons; and R^{12} represents alkyl of 1 - 4 carbons.

In the generalized formula (L), G represents $-PO_3H_2$, $-M$,



in which M represents $-CO_2H$, $-CON(R^{11})_2$, or $-CO_2R^{12}$, and R^{13} represents any of the side chains of the 19 noncyclic naturally occurring amino acids.

Pharmaceutically acceptable salts of the compounds falling within the generalized formula (L) are also within the invention.

The G unit is most preferably attached to the E unit at the carbon β to the D unit and is preferably a carboxylic acid group.

It is to be understood that as used herein, the term "alkyl" means straight, branched, cyclic, and polycyclic materials. The term "haloalkyl" means partially or fully halogenated alkyl groups such as $-(CH_2)_2Cl$, $-CF_3$, and $-C_6F_{13}$, for example.

In one of its embodiments, the invention relates to compounds of generalized formula (L) in which at least one of the units A, B, and R^6 comprises a heteroaromatic ring. Preferred heteroaromatic ring-containing compounds are those in which the heteroaryl groups are heteroaryl of 4 - 9 carbons comprising a 5 - 6 membered heteroaromatic ring containing O, S, or NR^1 when the ring is 5-membered, and N when said ring is 6-membered. Particularly preferred heteroaromatic ring-containing compounds are those in which at least one of the A and B units comprises a thiophene ring. When A unit is thiophene, it is preferably connected to B unit at position 2 and

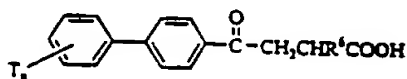
carries one substituent group T on position 5. When B unit is thiophene, it is preferably connected through positions 2 and 5 to D and A units respectively.

In the generalized formula (L), the A and B rings are preferably phenyl and phenylene, respectively. the A ring preferably bears at least one substituent group T preferably located on the position furthest from the position of the A ring which is connected to the B ring, the D unit is preferably a carbonyl group, and the G unit is preferably a carboxyl group.

In another embodiment, the invention relates to compounds of generalized formula (L), in the E unit of which n is 2 and m is 1. These compounds thus possess two carbon atoms between the D unit and the G unit, and carry one substituent on this two-carbon chain.

In another of its embodiments, the invention relates to compounds of generalized formula (L) in which the A ring is a substituted or unsubstituted phenyl group, the B ring is p-phenylene, and aryl portions of any aryl-containing R^6 moieties contain only carbon in the rings. These compounds thus contain no heteroaromatic rings.

In another of its embodiments, the invention relates to compounds of generalized formula (L) in which m is 1 and R^6 is an independent substituent. These compounds are materials which contain only a single substituent R^6 on the E unit, and this substituent is not involved in a ring. Preferred compounds within this subset have the formula



in which x is 1 and the substituent group T is located on the 4- position of the A ring, relative to the point of attachment between the A and B rings. The para substituent group T of this subset is more preferably acetylene containing moieties selected from the following group: $\text{MeOCH}_2\text{C}\equiv\text{C}-$, (*n*-

Pr)₂NCH₂C≡C-, CH₃CO₂CH₂C≡C-, EtOCO₂CH₂C≡C-, HOCH₂C≡C-, HO(CH₂)₂C≡C-, CH₃CO₂(CH₂)₂C≡C-, HO₂C(CH₂)₂C≡C-, OHC(CH₂)₂C≡C-, HO(CH₂)₄C≡C-, PhC≡C-, 3-HO-PhC≡C and PhCH₂OCH₂C≡C-.

Other compounds of general formula (L) in which R⁶ is -(CH₂)_tR⁷ have t as an integer of 1-5.

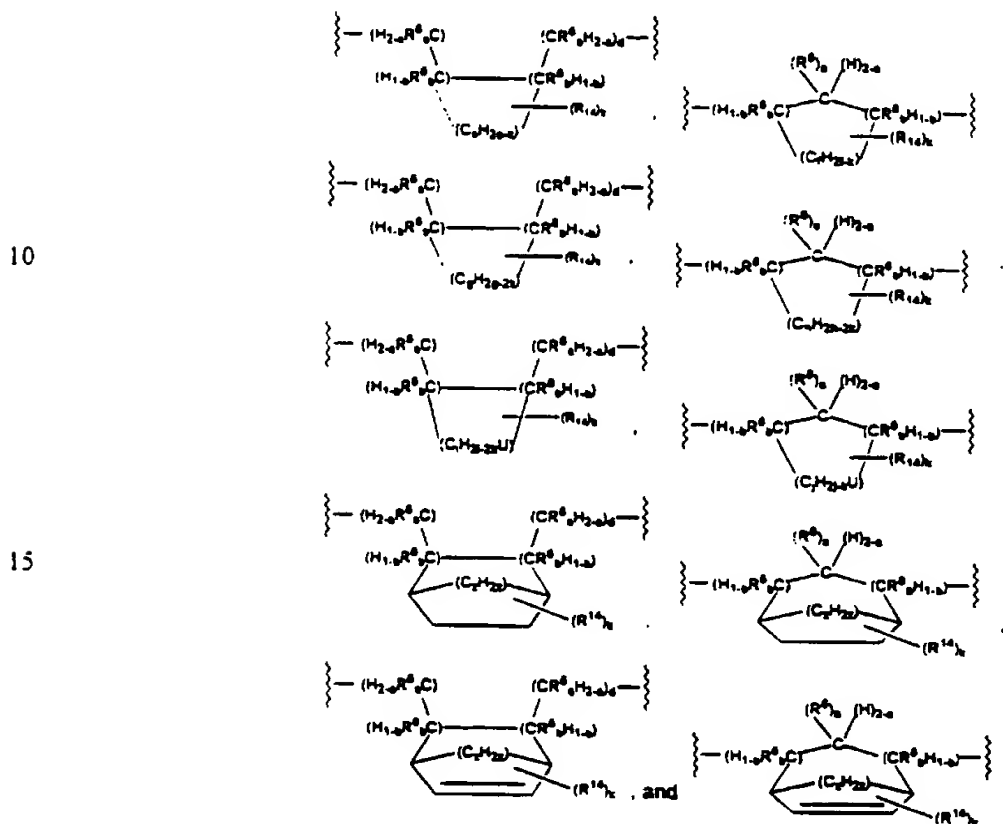
5 Preferred compounds of general formula (L) in which R⁶ is -(CH₂)_vZR⁸ have v as an integer of 1-4 and Z as -S- or -O-. Additional compounds of general formula (L) in which R⁶ is alkyl contain 4 or more carbons in said alkyl and those in which R⁶ is arylalkyl contain 2-3 carbons in the alkyl portion of said arylalkyl.

10 In another of its embodiments, the invention relates to compounds of generalized formula (L) in which the number of substituents m on the E unit is 2 or 3; and when m is 2, both groups R⁶ are independent substituents, or together constitute a spiro ring, or one group R⁶ is an independent substituent and the other constitutes a spiro ring; and when m is 3, two groups R⁶ are independent substituents and one group R⁶ constitutes a ring, or two groups R⁶ constitute a ring and one group R⁶ is an independent substituent, or three groups R⁶ are independent substituents. This subset
15 therefore contains compounds in which the E unit is di- or tri- substituted, and in the disubstituted case any rings formed by one or both R⁶ groups are spiro rings, and in the trisubstituted case, the R⁶ groups may form either spiro or nonspiro rings.

In another of its embodiments, the invention relates to compounds of generalized formula (L) in which the number of substituents m on the E unit is 1 or 2; and when m is 1, the group R⁶
20 constitutes a nonspiro ring; and when m is 2, both groups R⁶ together constitute a nonspiro ring or one group R⁶ is an independent substituent and the other constitutes a nonspiro ring. This subset

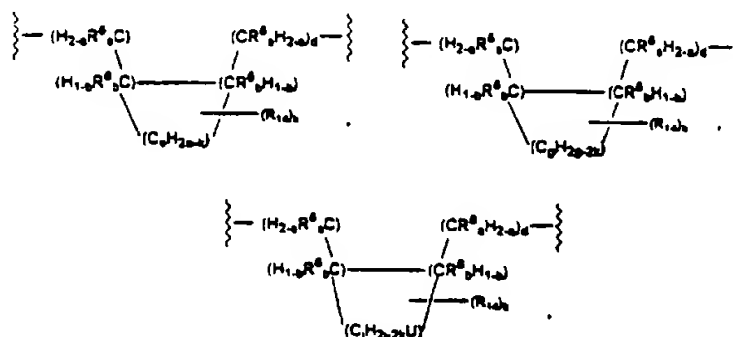
therefore contains compounds in which the E unit carries one or two substituents R^6 , and at least one of these substituents is involved in a nonspiro ring.

More particularly, representative compounds of generalized formula (L) in which one or more of the substituent groups R^6 are involved in formation of nonspiro rings have E units of the following structures:



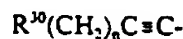
alkyl of 1 - 9 carbons; arylalkyl in which the alkyl portion contains 1 - 7 carbons and the aryl portion contains 6 - 10 carbons; alkenyl of 2 - 9 carbons; aryl-substituted alkenyl in which the alkenyl portion contains 2 - 4 carbons and the aryl portion contains 6 - 10 carbons; alkynyl of 2 - 9 carbons; aryl-substituted alkynyl in which the alkynyl portion contains 2 - 4 carbons and the aryl portion contains 6 - 10 carbons; aryl of 6 - 10 carbons; $-\text{COR}^2$; $-\text{CO}_2\text{R}^3$; $-\text{CON}(\text{R}^2)_2$; $-(\text{CH}_2)_t\text{R}^7$ in which t is 0 or an integer of 1 - 4; and $-(\text{CH}_2)_v\text{ZR}^8$ in which v is 0 or an integer of 1 to 3, and Z represents -S- or -O-. R^1 , R^7 , and R^8 have been defined above.

Preferred compounds of generalized formula (L) in which one or more of the substituent groups R^6 are involved in the formation of nonspiro rings have E units of the following structures:



in which a, b, c, d, (c + d), e, g, i, k, the total number of groups R^6 , U, and R^{14} are as defined above.

The substituent group T is preferably an acetylene containing moiety with the general formula:



where n is 1-4 and R^{30} is selected from the group consisting of: $\text{HO}-$, $\text{MeO}-$, $(n\text{-Pr})_2\text{N}-$, CH_3CO_2- , $\text{CH}_3\text{CH}_2\text{OCO}_2-$, $\text{HO}_2\text{C}-$, $\text{OHC}-$, $\text{Ph}-$, 3-HO-Ph- and $\text{PhCH}_2\text{O}-$, provided that when R^{30} is Ph or 3-HO-Ph, n = 0.

Most preferably, T is: $\text{MeOCH}_2\text{C}\equiv\text{C}-$, $(n\text{-Pr})_2\text{NCH}_2\text{C}\equiv\text{C}-$, $\text{CH}_3\text{CO}_2\text{CH}_2\text{C}\equiv\text{C}-$, $\text{EtOCO}_2\text{CH}_2\text{C}\equiv\text{C}-$, $\text{HOCH}_2\text{C}\equiv\text{C}-$, $\text{HO}(\text{CH}_2)_2\text{C}\equiv\text{C}-$, $\text{CH}_3\text{CO}_2(\text{CH}_2)_2\text{C}\equiv\text{C}-$, $\text{HO}_2\text{C}(\text{CH}_2)_2\text{C}\equiv\text{C}-$, $\text{OHC}(\text{CH}_2)_2\text{C}\equiv\text{C}-$, $\text{HO}(\text{CH}_2)_3\text{C}\equiv\text{C}-$, $\text{PhC}\equiv\text{C}-$, 3-HO-PhC $\equiv\text{C}-$ and $\text{PhCH}_2\text{OCH}_2\text{C}\equiv\text{C}-$.

The subscript x, which defines the number of T substituents, is preferably 1 or 2, most preferably 1, and when x is 1 the T is preferably on the 4- position of ring A.

The A ring is preferably a phenyl or thiophene ring, most preferably phenyl.

The B ring is preferably a 1,4-phenylene or 2,5-thiophene ring, most preferably 1,4-phenylene.

The D unit is most preferably a carbonyl group.

In the E group, R^6 is preferably:

1) arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

2) $-(\text{CH}_2)_t\text{R}'$ wherein t is 0 or an integer of 1 - 5 and R' is an imidoyl group containing an aromatic residue; or

3) $-(\text{CH}_2)_v\text{ZR}^8$ wherein v is 0 or an integer of 1 - 4, Z is S or O, and R^8 is aryl of 6 - 10 carbons or arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons.

The group R^6 is most preferably the following, wherein, any aromatic moiety is preferably substituted:

1) arylalkyl wherein the aryl portion is phenyl and the alkyl portion contains 1 - 4 carbons;

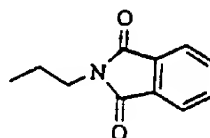
2) $-(CH_2)_tR^7$ wherein t is an integer 1 - 3, and R^7 is N-(1,2-naphthalene-dicarboximidoyl), N-(2,3-naphthalene-dicarboximidoyl), or N-(1,8-naphthalene-dicarboximidoyl); or N-phthalimidoyl.

3) $-(CH_2)_vZR^8$ wherein v is an integer of 1 - 3, Z is S, and R^8 is phenyl.

The more preferred compounds of generalized formula (L) have R^6 units of the following structures:



or



Those skilled in the art will appreciate that many of the compounds of the invention exist in enantiomeric or diastereomeric forms, and that it is understood by the art that such stereoisomers generally exhibit different activities in biological systems. This invention encompasses all possible stereoisomers which possess inhibitory activity against an MMP, regardless of their stereoisomeric designations, as well as mixtures of stereoisomers in which at least one member possesses inhibitory activity.

The most preferred compounds of the present invention are as indicated and named in the list below:

- I) R/S 4'-(3-hydroxy-1-propynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid,
- II) S- 4'-(3-hydroxy-1-propynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid,
- III) R-4'-(3-hydroxy-1-propynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid,
- IV) 4'-(3-methoxy-1-propynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid,
- V) γ -oxo- α -(3-phenylpropyl)-4'-(3-propyl-1-hexynyl)-[1,1'-biphenyl]-4-butanoic acid,

- VI) 4'-[3-(acetyloxy)-1-propynyl]- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- VII) 4'-[3-[(ethoxycarbonyloxy)-1-propynyl]- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- VIII) 4'-(4-hydroxy-1-butynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- 5 IX) 4'-[3-(acetyloxy)-1-propynyl]- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- X) 4'-(4-carboxy-1-butynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- XI) γ -oxo-4'-(5-oxo-1-pentynyl)- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- XII) 4'-(6-hydroxy-1-henynyl)- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- XIII) γ -oxo-4'-(phenylethynyl)- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid and
- 10 XIV) 4'-[3-hydroxyphenyl]ethynyl]- γ -oxo- α -(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid.
- XV) 1,3-dihydro-1,3-dioxo- α -[2-oxo-2-{4'-[3(phenylmethoxy)-1-propynyl][1,1'-biphenyl]-4-yl]ethyl]-2*H*-isoindole-2-butanoic acid. and
- XVI) 1,3-dihydro- α -[2-[4'-(hydroxyethynyl)[1,1'-biphenyl]-4-yl]-2-oxoethyl]-1,3-dioxo-2*H*-isoindole-2-butanoic acid.

15

General Preparative Methods:

The compounds of the invention may be prepared readily by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the inhibitors, with more detailed particular examples being

20 presented below in the experimental section describing the working examples. All variable groups of these methods are as described in the generic description if they are not specifically defined below. The variable subscript *n* is independently defined for each method. When a variable group

with a given symbol (i.e R⁹) is used more than once in a given structure, it is to be understood that each of these groups may be independently varied within the range of definitions for that symbol.

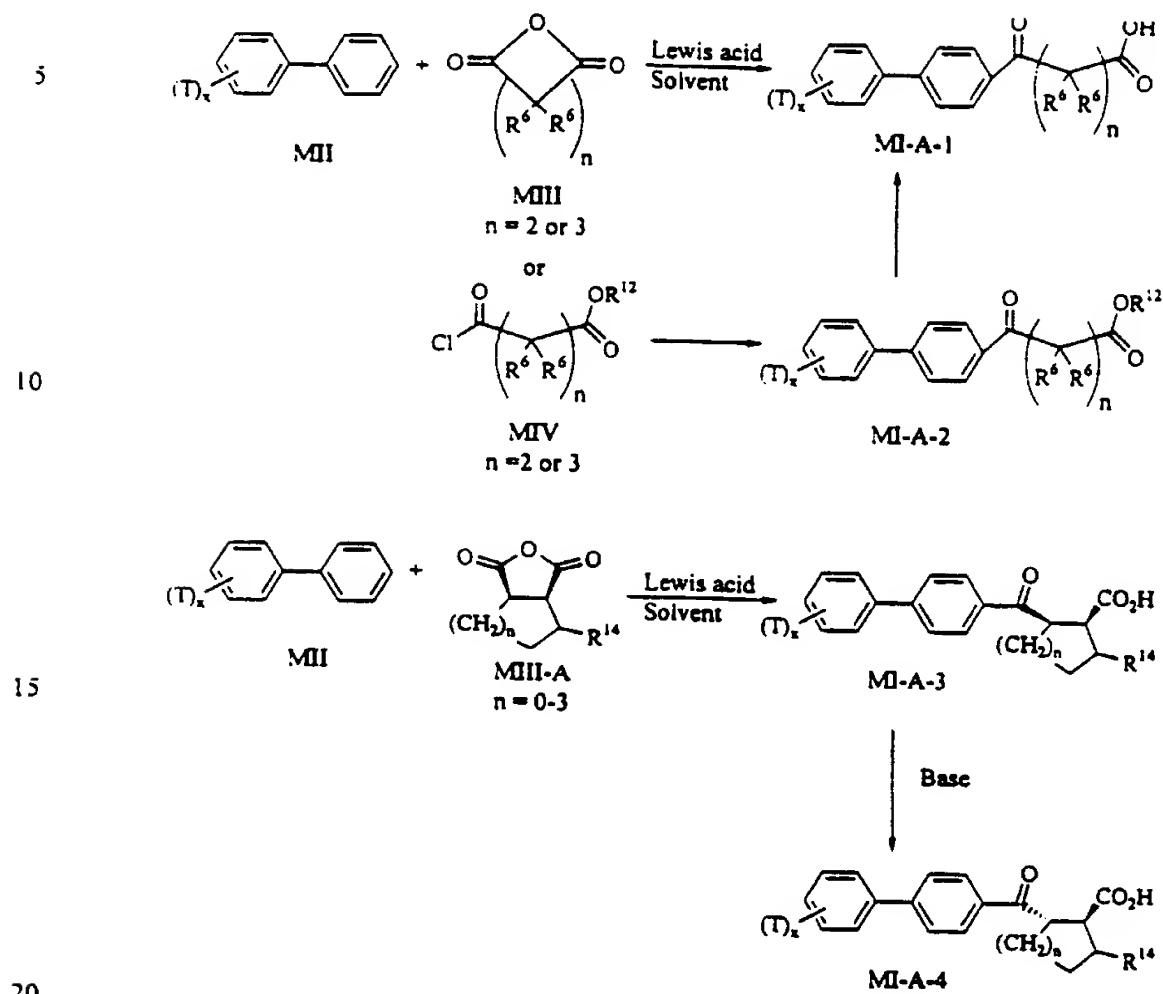
General Method A - The compounds of this invention in which the rings A and B are substituted phenyl and phenylene respectively are conveniently prepared by use of a Friedel-Crafts reaction of a substituted biphenyl MII with an activated acyl-containing intermediate such as the succinic or glutaric anhydride derivative MIII or acid chloride MIV in the presence of a Lewis acid catalyst such as aluminum trichloride in an aprotic solvent such as 1,1,2,2-tetrachloroethane. The well known Friedel-Crafts reaction can be accomplished with use of many alternative solvents and acid catalysts as described by Berliner, Org. React., 2, 229, 1949 and Heaney, Comp. Org. Synth. 2, 733, 1991.

If the anhydride MIII is monosubstituted or multiply-substituted in an unsymmetrical way, the raw product MI-A often exists as a mixture of isomers via attack of the anhydride from either of the two carbonyls. The resultant isomers can be separated into pure forms by crystallization or chromatography using standard methods known to those skilled in the art.

When they are not commercially available, the succinic anhydrides MIII can be prepared via a Stobbe Condensation of a dialkyl succinate with an aldehyde or ketone (resulting in side chain R⁶), followed by catalytic hydrogenation, hydrolysis of a hemiester intermediate to a diacid, and then conversion to the anhydride MIII by reaction with acetyl chloride or acetic anhydride. Alternatively, the hemiester intermediate is converted by treatment with thionyl chloride or oxalyl chloride to the acid chloride MIV. For a review of the Stobbe condensation, including lists of suitable solvents and bases see Johnson and Daub, Org. React. 6, 1, 1951.

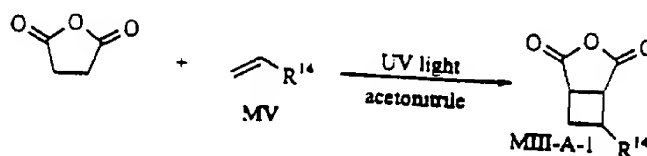
This method, as applied to the preparation of MIII ($R^6 = H, \text{isobutyl and } H, n\text{-pentyl}$), has been described Wolanin, et al., US Patent 4,771,038.

Method A



Method A is especially useful for the preparation of cyclic compounds such as MI-A-3, in which two R^6 groups are connected in a methylene chain to form a 3-7 member ring. Small ring (3-5

member) anhydrides are readily available only as cis isomers which yield cis invention compounds
 MII-A-3. The trans compounds MII-A-4 are then prepared by treatment of MII-A-3 with a base such
 as DBU in THF. The substituted four member ring starting material anhydrides such as MIII-A-1
 are formed in a photochemical 2-2 reaction as shown below. This method is especially useful for
 the preparation of compounds in which R¹⁴ is acetoxy or acetoxyethylene. After the subsequent
 Friedel-Crafts reaction the acetate can be removed by basic hydrolysis and the carboxyl protected
 by conversion to 2-(trimethylsilyl)ethyl ester. The resultant intermediate with R¹⁴ = CH₂OH can
 be converted to invention compounds with other R¹⁴ groups by using procedures described in
 General Method G.



The Friedel-Crafts method is also useful when double bonds are found either between C-2
 and C-3 of a succinoyl chain (from maleic anhydride or 1-cyclopentene-1,2-dicarboxylic anhydride,
 for example) or when a double bond is found in a side chain, such as in the use of itaconic anhydride
 as starting material to yield products in which two R⁶ groups are found on one chain carbon together
 to form an exo-methylene (=CH₂) group. Subsequent uses of these compounds are described in
 Methods D.

General Method B - Alternatively the compounds MI can be prepared via a reaction
 sequence involving mono-alkylation of a dialkyl malonate MVI with an alkyl halide to form
 intermediate MVII, followed by alkylation with a halomethyl biphenyl ketone MVIII to yield
 intermediate MIX. Compounds of structure MIX are then hydrolyzed with aqueous base and heated

to decarboxylate the malonic acid intermediate and yield MI-B-2 (Method B-1). By using one equivalent of aqueous base the esters MI-B-2 with R^{12} as alkyl are obtained, and using more than two equivalents of base the acid compounds ($R^{12} = H$) are obtained. Optionally, heat is not used and the diacid or acid-ester MI-B-1 is obtained.

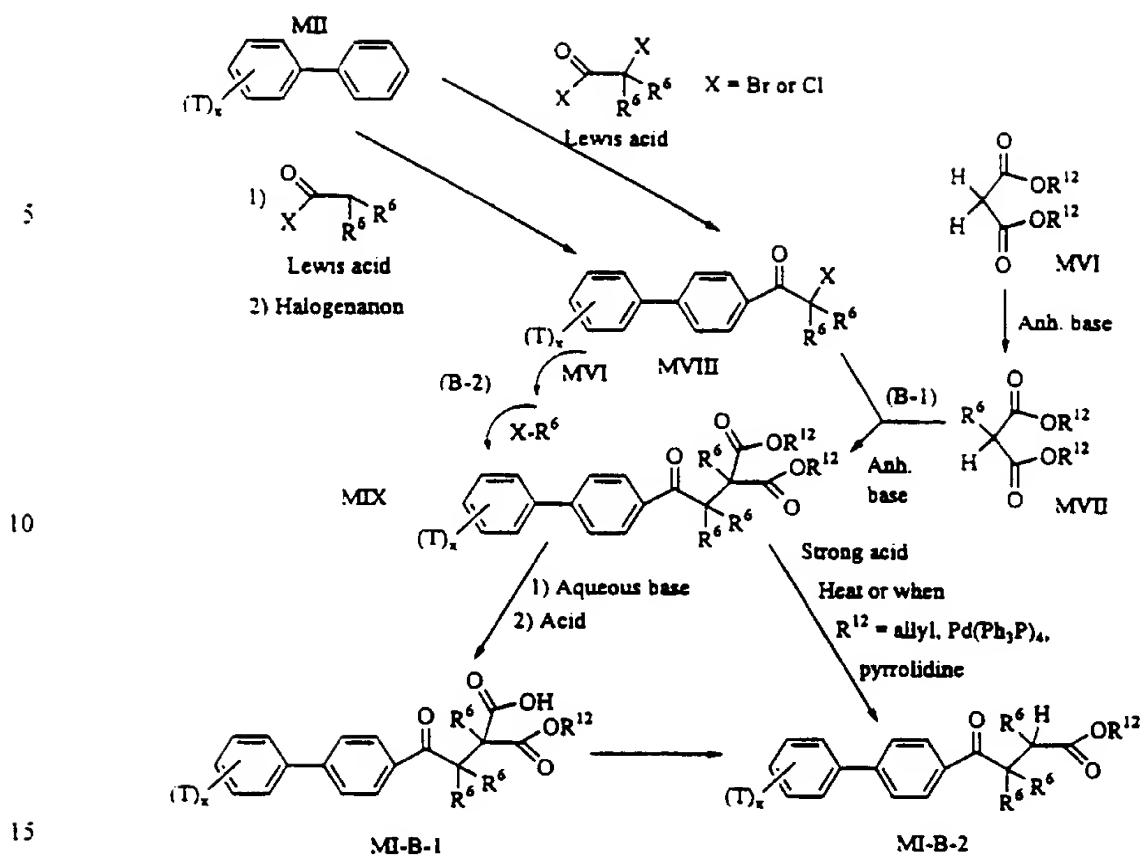
5 Alternatively, the diester intermediate MIX can be heated with a strong acids such as concentrated hydrochloric acid in acetic acid in a sealed tube at about 110 °C for about 24 hr to yield MI-B-1 ($R^{12} = H$). Alternatively, the reaction of MVI with MVIII can be conducted before that with the alkyl halide to yield the same MIX (Method B-2).

Alternatively, a diester intermediate MXIX, which contains $R^{12} = \text{allyl}$, can be exposed to Pd catalysts in the presence of pyrrolidine to yield MI-B-2 ($R^{12} = H$) (Deziel, Tetrahedron Lett. 28, 4371, 1990).

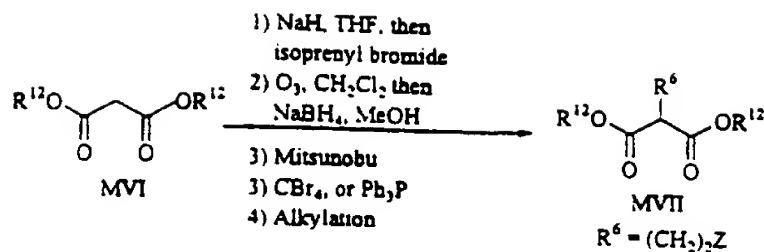
Intermediates MVII are formed from biphenyls MII in a Friedel-Craft reaction with haloacetyl halides such as bromoacetyl bromide or chloroacetyl chloride. Alternatively, the biphenyl can be reacted with acetyl chloride or acetic anhydride and the resultant product halogenated with, for example, bromine to yield intermediates MVIII ($X = Br$).

15 Method B has the advantage of yielding single regio isomers when Method A yields mixtures. Method B is especially useful when the side chains R^6 contain aromatic or heteroaromatic rings that may participate in intramolecular acylation reactions to give side products if Method A were to be used. This method is also very useful when the R^6 group adjacent to the carboxyl of the final compound contains heteroatoms such as oxygen, sulfur, or nitrogen, or more complex functions such as imide rings.

METHOD B



When R^6 contains selected functional groups Z, malonate MVII can be prepared by alkylating a commercially available unsubstituted malonate with prenyl or allyl halide, subject this product to ozonolysis with reductive work-up, and the desired z group can be coupled *via* a Mitsunobu reaction (Mitsunobu, Synthesis 1, 1981). Alternatively, the intermediate alcohol can be subjected to alkylation conditions to provide malonate MVII containing the desired Z group.



5

General Method C - Especially useful is the use of chiral HPLC to separate the enantiomers of racemic product mixtures (see, for example, Arit, et al., Chem. Int. Ed. Engl. 12, 30, 1991). The compounds of this invention can be prepared as pure enantiomers by use of a chiral auxiliary route. See, for example, Evans, Aldrichimica Acta, 15(2), 23, 1982 and other similar references known to one skilled in the art.

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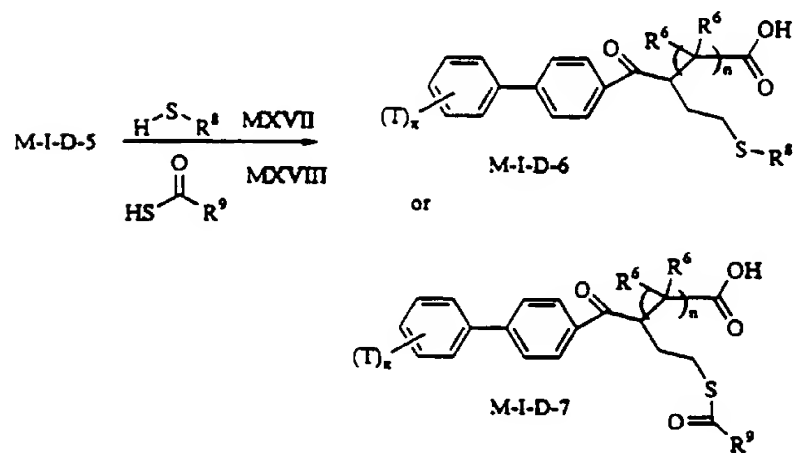
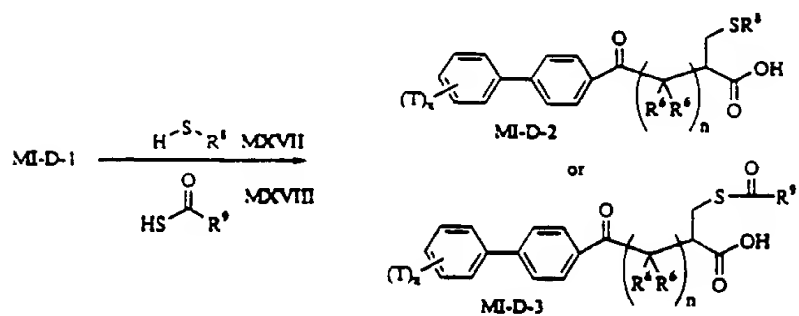
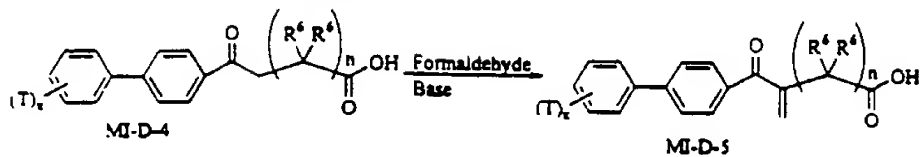
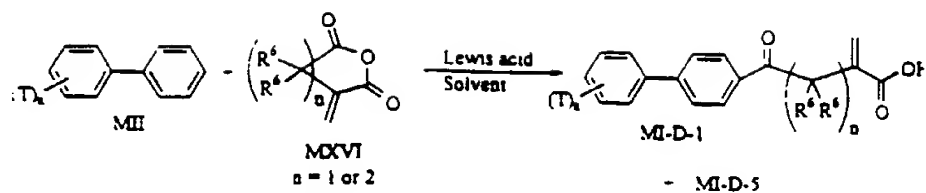
General Method D - Compounds in which R⁶ are alkyl- or aryl- or heteroaryl- or acyl- or heteroarylcarbonyl-thiomethylene are prepared by methods analogous to those described in the patent WO 90/05719. Thus substituted itaconic anhydride MXVI (n = 1) is reacted under Friedel-Crafts conditions to yield acid MI-D-1 which can be separated by chromatography or crystallization from small amounts of isomeric MI-D-5. Alternatively, MI-D-5s are obtained by reaction of invention compounds MI-D-4 (from any of Methods A through C) with formaldehyde in the presence of base.

15

Compounds MI-D-1 or MI-D-5 are then reacted with a mercapto derivative MXVII or MXVIII in the presence of catalyst such as potassium carbonate, ethyldiisobutylamine, tetrabutylammonium fluoride or free radical initiators such as azobisisobutyronitrile (AIBN) in a solvent such as diethylformamide or tetrahydrofuran to yield invention compounds MI-D-2, MI-D-3, MI-D-6, or MI-D-7.

20

Method D



General Method E - Biaryl compounds such as those of this application may also be prepared by Suzuki or Stille cross-coupling reactions of aryl or heteroaryl metallic compounds in which the metal is zinc, tin, magnesium, lithium, boron, silicon, copper, cadmium or the like with an aryl or heteroaryl halide or triflate (trifluoromethane-sulfonate) or the like. In the equation below either
 5 Met or X is the metal and the other is the halide or triflate (OTf). Pd(com) is a soluble complex of palladium such as tetrakis(triphenylphosphine)-palladium(O) or bis- (triphenylphosphine)-palladium(III) chloride. These methods are well known to those skilled in the art. See, for example, Suzuki, Pure Appl. Chem. 63, 213, 1994; Suzuki, Pure Appl. Chem. 63, 419, 1991; and Farina and Roth, "Metal-Organic Chemistry" Volume 5 (Chapter 1), 1994.

10 The starting materials MXXIII (B = 1,4-phenylene) are readily formed using methods analogous to those of methods A, B, C, or D but using a halobenzene rather than a biphenyl as starting material. When desired, the materials in which X is halo can be converted to those in which X is metal by reactions well known to those skilled in the art, such as treatment of a bromo intermediate with hexamethylditin and palladium tetrakis(triphenylphosphine) in toluene at reflux to
 15 yield the trimethyltin intermediate. The starting materials MXXIII (B = heteroaryl) are most conveniently prepared by method C but using readily available heteroaryl rather than biphenyl starting materials. The intermediates MXXII are either commercial or easily prepared from commercial materials by methods well known to those skilled in the art.

Method E



T, x, A, B, E and G as in Structure (L)

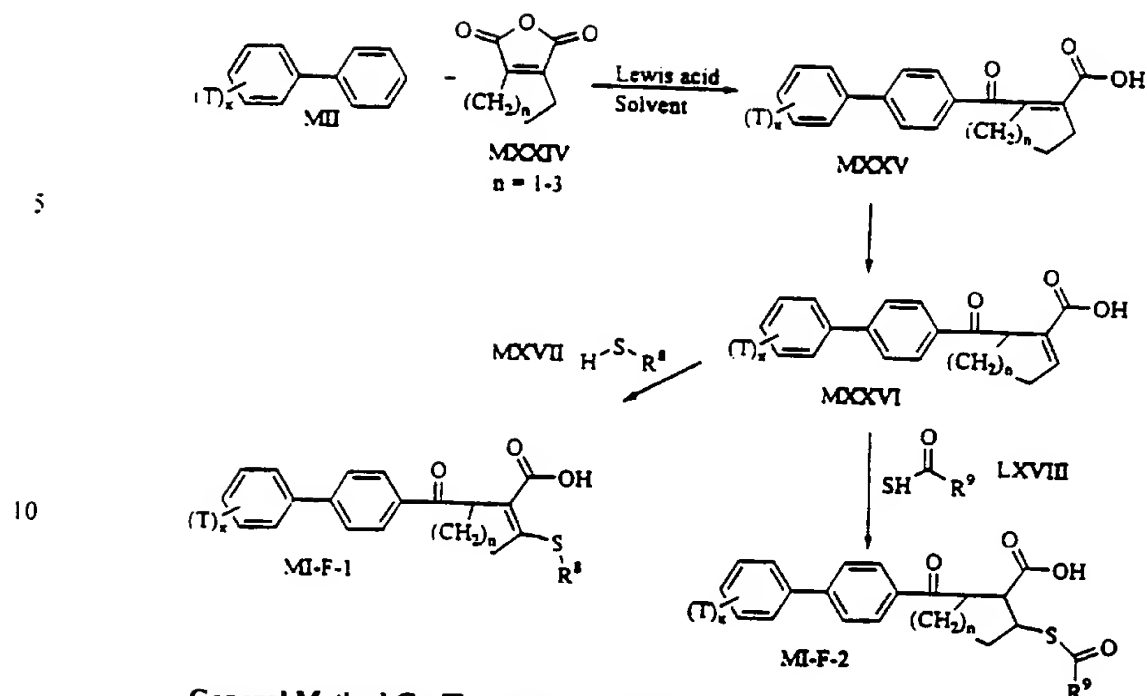
Met = Metal and X = Halide or Triflate

or
Met = Halide or Triflate and X = Metal

These general methods are useful for the preparation of compounds for which Friedel-Crafts reactions such as those of Methods A, B, C, or D would lead to mixtures with various biaryl acylation patterns. Method E is also especially useful for the preparation of products in which the aryl groups A or B contain one or more heteroatoms (heteroaryls) such as those compounds that contain thiophene, furan, pyridine, pyrrole, oxazole, thiazole, pyrimidine or pyrazine rings or the like instead of phenyls.

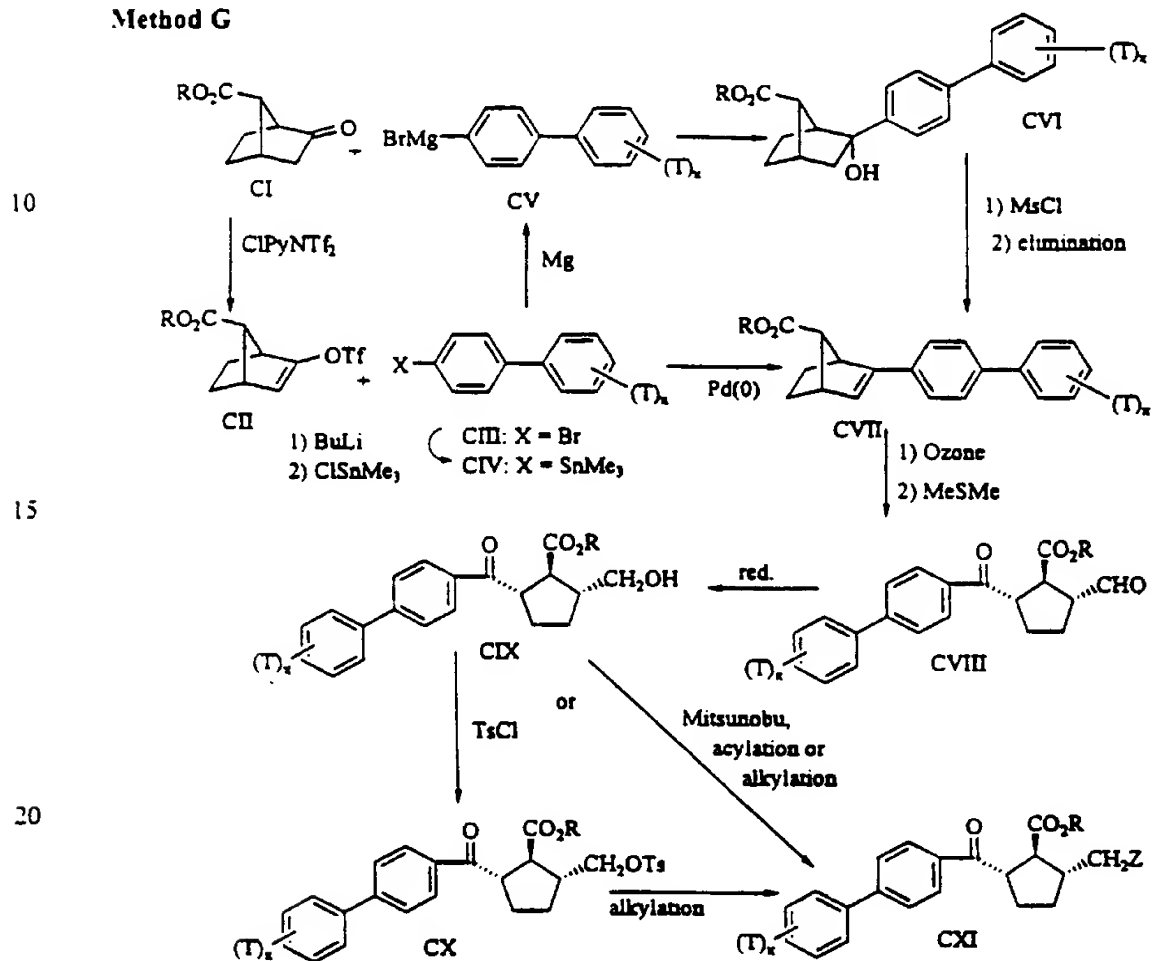
General Method F - When the R⁶ groups of method F form together a 4 - 7 member carbocyclic ring as in Intermediate MXXV below, the double bond can be moved out of conjugation with the ketone group by treatment with two equivalents of a strong base such as lithium diisopropylamide or lithium hexamethylsilylamide or the like followed by acid quench to yield compounds with the structure MXXVI. Reaction of MXXVI with mercapto derivatives using methods analogous to those of General Method D then leads to cyclic compounds MI-F-1 or MI-F-2.

Method F



General Method G - The compounds of this invention in which two R^6 groups are joined to form a substituted 5-member ring are most conveniently prepared by method G. In this method acid CII ($R = H$) is prepared using the protocols described in Tetrahedron 37, Suppl., 411, 1981. The acid is protected as an ester [eg. $R =$ benzyl (Bn) or 2-(trimethylsilyl)ethyl (TMSE)] by use of coupling agents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and procedures well known to those skilled in the art. Substituted bromobiphenyl CIII is converted to its Grignard reagent by treatment with magnesium and reacted with CI to yield alcohol CVI. Alcohol CVI is eliminated via base treatment of its mesylate by using conditions well known to those skilled in the art to yield olefin CVII. Alternatively CIII is converted to a trimethyltin intermediate via initial metallation of the bromide with n-butyllithium at low temperature (-78°C)

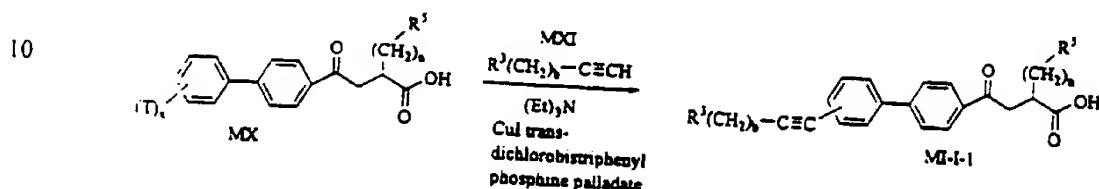
followed by treatment with chlorotrimethyltin and Cl is converted to an enoltriflate (CII) by reaction with 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine in the presence of a strong aprotic base. The tin and enoltriflate intermediates are then coupled in the presence of a Pd⁰ catalyst, CuI and AsPh₃ to yield directly intermediate CVII. Ozonolysis of CVII (workup with methylsulfide) yields aldehyde CVIII. Alternatively treatment with OsO₄, followed by HIO₄, converts CVII to CVIII.

Method G

Conversion of key intermediate CVIII to the targeted patent compounds is accomplished in several ways depending on the identity of side chain function Z. Reaction of CVIII with Wittig reagents followed by hydrogenation yields products in which Z is alkyl and or arylalkyl. Selective reduction of aldehyde CVIII with a reducing agent such as lithium tris [(3-ethyl-
5 3pentyl)oxy]aluminum hydride (LTEPA) yields alcohol CX. The alcohol is converted to phenyl ethers or a variety of heteroatom substituted derivatives used to generate sidechain Z via the Mitsunobu conditions well known to those skilled in the art (see Mitsunobu, Synthesis, 1, 1981). Alternatively the alcohol of CX is converted to a leaving group such as tosylate (CX) or bromide by conditions well known to those skilled in the art and then the leaving group is displaced by an
10 appropriate nucleophile. Several examples of this type of reaction can be found in Norman, et al., J. Med. Chem. 37, 2552, 1994. Direct acylation of the alcohol CX yields invention compounds in which Z = OAcyl and reaction of the alcohol with various alkyl halides in the presence of base yields alkyl ethers. In each case a final step is removal of acid blocking group R to yield acids (R = H) by using conditions which depend on the stability of R and Z, but in all cases well known to
15 those skilled in the art such as removal of benzyl by base hydrolysis or of 2-(trimethylsilyl)ethyl by treatment with tetrabutylammonium fluoride.

General Method H - Amides of the acids of the invention compounds can be prepared from the acids by treatment in an appropriate solvent such as dichloromethane or dimethylformamide with a primary or secondary amine and a coupling agent such as dicyclohexylcarbodiimide. These
20 reactions are well known to those skilled in the art. The amine component can be simple alkyl or arylalkyl substituted or can be amino acid derivatives in which the carboxyl is blocked and the amino group is free.

General Method I - The compounds of this invention in which (T)_x is an alkynyl or substituted alkynyl are prepared according to general method I (Austin, J. Org. Chem. 46, 2280, 1981). Intermediate MX is prepared according to methods A, B, C, D or G by starting with commercial MIII (R¹ = Br). Reaction of MX with substituted acetylene MXI in the presence of Cu(I) / palladate reagent gives invention compound MI-I-1. In certain cases, R¹ may be an alcohol blocked as trialkylsilyl. In such cases the silyl group can be removed by treatment with acids such as trifluoroacetic acid or HF - pyridine reagent.

Method I

Suitable pharmaceutically acceptable salts of the compounds of the present invention include addition salts formed with organic or inorganic bases. The salt forming ion derived from such bases can be metal ions, e.g., aluminum, alkali metal ions, such as sodium or potassium, alkaline earth metal ions such as calcium or magnesium, or an amine salt ion, of which a number are known for this purpose. Examples include ammonium salts, arylalkylamines such as dibenzylamine and *N,N*-dibenzylethylenediamine, lower alkylamines such as methylamine, *t*-butylamine, procaine, lower alkylpiperidines such as *N*-ethylpiperidine, cycloalkylamines such as cyclohexylamine or dicyclohexylamine, 1-adamantylamine, benzathine, or salts derived from amino acids like arginine, lysine or the like. The physiologically acceptable salts such as the sodium or potassium salts and the amino acid salts can be used medicinally as described below and are preferred.

These and other salts which are not necessarily physiologically acceptable are useful in isolating or purifying a product acceptable for the purposes described below. For example, the use of commercially available enantiomerically pure amines such as (+)-cinchonine in suitable solvents can yield salt crystals of a single enantiomer of the invention compounds, leaving the opposite enantiomer in solution in a process often referred to as "classical resolution." As one enantiomer of a given invention compound is usually substantially greater in physiological effect than its antipode, this active isomer can thus be found purified in either the crystals or the liquid phase. The salts are produced by reacting the acid form of the invention compound with an equivalent of the base supplying the desired basic ion in a medium in which the salt precipitates or in aqueous medium and then lyophilizing. The free acid form can be obtained from the salt by conventional neutralization techniques, e.g., with potassium bisulfate, hydrochloric acid, etc.

The compounds of the present invention have been found to inhibit the matrix metalloproteases MMP-3, MMP-9 and MMP-2, and to a lesser extent MMP-1, and are therefore useful for treating or preventing the conditions referred to in the background section. As other MMPs not listed above share a high degree of homology with those listed above, especially in the catalytic site, it is deemed that compounds of the invention should also inhibit such other MMPs to varying degrees. Varying the substituents on the biaryl portions of the molecules, as well as those of the propanoic or butanoic acid chains of the claimed compounds, has been demonstrated to affect the relative inhibition of the listed MMPs. Thus compounds of this general class can be "tuned" by selecting specific substituents such that inhibition of specific MMP(s) associated with specific pathological conditions can be enhanced while leaving non-involved MMPs less affected.

The method of treating matrix metalloprotease-mediated conditions may be practiced in mammals, including humans, that exhibit such conditions.

The inhibitors of the present invention are contemplated for use in veterinary and human applications. For such purposes, they will be employed in pharmaceutical compositions containing active ingredient(s) plus one or more pharmaceutically acceptable carriers, diluents, fillers, binders, and other excipients, depending on the administration mode and dosage form contemplated.

Administration of the inhibitors may be by any suitable mode known to those skilled in the art. Examples of suitable parenteral administration include intravenous, intraarticular, subcutaneous and intramuscular routes. Intravenous administration can be used to obtain acute regulation of peak plasma concentrations of the drug. Improved half-life and targeting of the drug to the joint cavities may be aided by entrapment of the drug in liposomes. It may be possible to improve the selectivity of liposomal targeting to the joint cavities by incorporation of ligands into the outside of the liposomes that bind to synovial-specific macromolecules. Alternatively intramuscular, intraarticular or subcutaneous depot injection with or without encapsulation of the drug into degradable microspheres e.g., comprising poly(DL-lactide-co-glycolide) may be used to obtain prolonged sustained drug release. For improved convenience of the dosage form it may be possible to use an i.p. implanted reservoir and septum such as the Percuseal system available from Pharmacia. Improved convenience and patient compliance may also be achieved by the use of either injector pens (e.g. the Novo Pin or Q-pen) or needle-free jet injectors (e.g. from Bioject, Mediject or Becton Dickinson). Prolonged zero-order or other precisely controlled release such as pulsatile release can also be achieved as needed using implantable pumps with delivery of the drug through a cannula

into the synovial spaces. Examples include the subcutaneously implanted osmotic pumps available from ALZA, such as the ALZET osmotic pump.

5 Nasal delivery may be achieved by incorporation of the drug into bioadhesive particulate carriers ($<200 \mu\text{m}$) such as those comprising cellulose, polyacrylate or polycarbophil, in conjunction with suitable absorption enhancers such as phospholipids or acylcarnitines. Available systems include those developed by DanBiosys and Scios Nova.

10 A noteworthy attribute of the compounds of the present invention in contrast to those of various peptidic compounds referenced in the background section of this application is the demonstrated oral activity of the present compounds. Certain compounds have shown oral bioavailability in various animal models of up to 90 - 98 %. Oral delivery may be achieved by incorporation of the drug into tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. Oral delivery may also be achieved by incorporation of the drug into enteric coated capsules designed to release the drug into the colon where digestive protease activity is low. Examples include the OROS-CT/Osmer™ and PULSINCAP™ systems from ALZA and Scherer Drug Delivery Systems respectively. Other systems use azo-crosslinked polymers that are degraded by colon specific bacterial azoreductases, or pH sensitive polyacrylate polymers that are activated by the rise in pH at the colon. The above systems may be used in conjunction with a wide range of available absorption enhancers.

Rectal delivery may be achieved by incorporation of the drug into suppositories.

20 The compounds of this invention can be manufactured into the above listed formulations by the addition of various therapeutically inert, inorganic or organic carriers well known to those skilled in the art. Examples of these include, but are not limited to, lactose, corn starch or derivatives

thereof, talc, vegetable oils, waxes, fats, polyols such as polyethylene glycol, water, saccharose, alcohols, glycerin and the like. Various preservatives, emulsifiers, dispersants, flavorants, wetting agents, antioxidants, sweeteners, colorants, stabilizers, salts, buffers and the like are also added, as required to assist in the stabilization of the formulation or to assist in increasing bioavailability of the active ingredient(s) or to yield a formulation of acceptable flavor or odor in the case of oral dosing.

The amount of the pharmaceutical composition to be employed will depend on the recipient and the condition being treated. The requisite amount may be determined without undue experimentation by protocols known to those skilled in the art. Alternatively, the requisite amount may be calculated, based on a determination of the amount of target enzyme which must be inhibited in order to treat the condition.

The matrix metalloprotease inhibitors of the invention are useful not only for treatment of the physiological conditions discussed above, but are also useful in such activities as purification of metalloproteases and testing for matrix metalloprotease activity. Such activity testing can be both *in vitro* using natural or synthetic enzyme preparations or *in vivo* using, for example, animal models in which abnormal destructive enzyme levels are found spontaneously (use of genetically mutated or transgenic animals) or are induced by administration of exogenous agents or by surgery which disrupts joint stability.

EXAMPLES

The following examples are offered for illustrative purposes only and are not intended, nor should they be construed, to limit the invention in any way.

General Procedures:

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated using a Buchi evaporator unless otherwise indicated.

Materials:

Commercial grade reagents and solvents were used without further purification except that diethyl ether and tetrahydrofuran were usually distilled under argon from benzophenone ketyl, and methylene chloride was distilled under argon from calcium hydride. Many of the specialty organic or organometallic starting materials and reagents were obtained from Aldrich, 1001 West Saint Paul Avenue, Milwaukee, WI 53233. Solvents are often obtained from EM Science as distributed by VWR Scientific.

Chromatography:

Analytical thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60 A F-254 250 μ m plates. Visualization of spots was effected by one of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and (d) immersion of the plate in a 3% solution of p-anisaldehyde in ethanol containing 0.5% concentrated sulfuric acid followed by heating.

Column chromatography was performed using 230-400 mesh EM Science® silica gel.

Analytical high performance liquid chromatography (HPLC) was performed at 1 mL min⁻¹ on a 4.6 x 250 mm Microsorb[®] column monitored at 288 nm, and semi-preparative HPLC was performed at 24 mL min⁻¹ on a 21.4 x 250 mm Microsorb[®] column monitored at 288 nm.

5 **Instrumentation:**

Melting points (mp) were determined with a Thomas-Hoover melting point apparatus and are uncorrected.

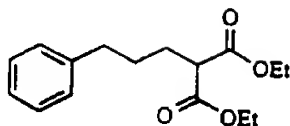
Proton (¹H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-OMEGA 300 (300 MHz) spectrometer, and carbon thirteen (¹³C) NMR spectra were
10 measured with a General Electric GN-OMEGA 300 (75 MHz) spectrometer. Most of the compounds synthesized in the experiments below were analyzed by nmr, and the spectra were consistent with the proposed structures in each case.

Mass spectral (MS) data were obtained on a Kratos Concept 1-H spectrometer by liquid-caesium secondary ion (LCIMS), an updated version of fast atom bombardment (FAB). Most
15 of the compounds synthesized in the experiments below were analyzed by mass spectroscopy, and the spectra were consistent with the proposed structures in each case.

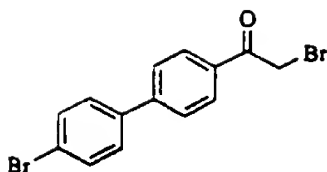
General Comments:

For multi-step procedures, sequential steps are noted by numbers.

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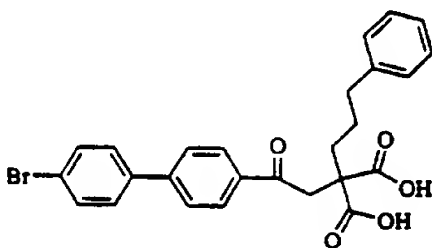
Example 1- Preparation of Compound I

5 **Step 1** A dry 2-L, three-necked, round-bottomed flask was equipped with a stir bar, a pressure equalizing addition funnel, an argon inlet and a thermometer. The flask was charged with a suspension of sodium hydride (8.4 g of 95% NaH; -0.33 mol) in dry THF (700 mL) and was cooled with an ice water bath. Diethyl malonate (48.54 g, 0.30 mol) was added dropwise from the addition
10 funnel over 25 min. Stirring was continued for 1.5 h before adding 1-bromo-3-phenylpropane (47 mL, ~61 g, -0.30 mol) over 10 min via the addition funnel. Rinses of the addition funnel (THF, 2 x 10 mL) were added to the reaction mixture and stirring was continued for 30 min. The addition funnel and thermometer were replaced with a reflux condenser and stopper, and the reaction was heated at reflux for 19 h. The mixture was cooled to room temperature and then with an ice water bath. Distilled water (400 mL) was slowly added with stirring. The layers were separated and the
15 aqueous phase was extracted with chloroform (100 mL). The combined organics were washed with 10% HCl (250 mL) and the separated aqueous phase was back-extracted with chloroform (100 mL). The combined organics were washed with saturated NaHCO₃ (250 mL) and the separated aqueous phase was back-extracted with chloroform (100 mL). The organics were dried (Na₂SO₄) and concentrated to yield a yellow oil which was purified by distillation through a Vigreux column at
20 reduced pressure (0.4 torr). The fraction boiling at 124-138 °C was clean desired product (57.21 g, 0.206 mol; 68% yield). TLC (50% hexanes-dichloromethane): R_f = 0.32.



- 5 **Step 2** A 1-L, one-necked, round bottom flask was equipped with a rubber septum and an argon inlet. The flask was charged with a solution of commercially available 4-bromobiphenyl (50.00g, 0.215 mol) in dichloromethane (100mL). Bromoacetyl bromide (21.0mL, 48.7g, 0.230 mol) was added via syringe and the solution was cooled with an ice water bath to 0 °C, while AlCl₃ (34.3g, 0.258 mol) was added portionwise. Gas evolved from the opaque olive green reaction mixture.
- 10 After 24h at room temperature, the reaction mixture was cautiously poured into a cold saturated aqueous NaHCO₃ solution. The resulting mixture was extracted with three 200mL portions of ethyl acetate, and the combined organic layers were dried over Na₂SO₄ and concentrated to afford the desired product as a yellow solid in quantitative yield. TLC (30% dichloromethane-hexanes), R_f = 0.30.

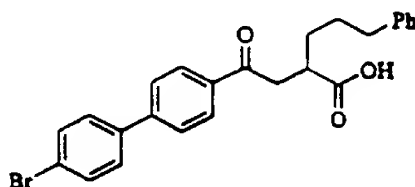
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- 20 **Step 3** A dry 2-L, three-necked, round-bottomed flask was equipped with a magnetic stir bar, an argon inlet, and a pressure equalizing addition funnel. The flask was charged with a solution of the product of step 1 (63.0 g, 0.227 mol) in THF (500 mL). The reaction vessel was cooled with an ice

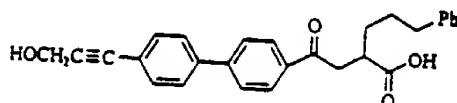
water bath while sodium hydride (5.40 g of 95% NaH, 0.214 mol) was added slowly in portions. The reaction mixture was stirred for 1 h at 0 °C, and a solution of the product of step 2 (80.0 g, 0.215 mol) in dry THF (300 mL) was added via addition funnel over ca. 20 min. The deep orange reaction mixture was stirred at room temperature under argon for 3 h. The reaction vessel was cooled in an ice water bath while distilled water (150 mL) was added cautiously. The aqueous phase was extracted with three 300 mL portions of ethyl acetate, the combined organic phases were dried over MgSO₄, and concentrated to afford 124 g of a dark orange oil. This material was used in the following operation without purification.

The orange oil was dissolved in 400 mL of 1:1 THF:methanol, and added to an aqueous NaOH solution (4 N, 500 mL, 2.00 mol). The reaction mixture was stirred for 24 h at room temperature, 48 h at 50 °C, and 24 hours at room temperature. The majority of MeOH was removed *in vacuo* and the residue extracted with a 200 mL portion of 1:1 ethyl acetate:hexanes and a 200 mL portion of hexanes. The aqueous phase was acidified with HCl, extracted with two 200 mL portions, and three 100 mL portions of ethyl acetate. The combined organic phases were dried over MgSO₄, and concentrated to afford a quantitative yield of diacid. TLC (10% methanol-chloroform with 1% acetic acid): R_f=0.45.



Step 4 The unpurified diacid from step 3 was dissolved in 1,4-dioxane (500 mL) and heated to reflux for 24 h. The solvent was removed *in vacuo*, and a 10 g portion of the residue

chromatographed on silica gel (gradient elution with 10-50% ethyl acetate-hexanes containing 1% acetic acid) to afford 0.840 g (10%) of the desired product as a yellow solid. MP 174 °C.



5

Step 5 - A one-necked, 15-mL. round-bottomed flask equipped with a rubber septum and an argon needle inlet was charged with 2.6 mL of diethylamine, the product of step 4 (0.300 g, 0.667 mmol), propargyl alcohol (1.0 mL, 0.96 g, 17 mmol), copper (I) iodide (0.0220 g, 0.115 mmol), and *trans*-dichlorobis(triphenylphosphine)palladate (0.110 g, 0.157 mmol). The resulting mixture was stirred for 4 d at room temperature. The reaction mixture was concentrated (290 mg residue) and part of the residue (90 mg) was purified via column chromatography on 50 g of silica gel (20% ethyl acetate-hexanes with 0.5% acetic acid) afforded the coupling product as a white solid (0.035 g, 40%) of coupling product as a white solid. MP 130 °C.

10

15 Example 2 and Example 3 - Preparation of Compounds II and III

Example 2 and Example 3 were prepared by chiral separation of Example 1 on a Chiralcel AD[®] column (2 cm x 25 cm) using 5% EtOH, 4.75% H₂O and 0.095% HOAc in CH₃CN, flow rate 20 mL/min.

Example 2: First off Chiralcel AD[®] column; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.17-7.33 (m, 5 H), 4.54 (s, 2 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.14-3.02 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.64-1.84 (m, 4 H).

20

Example 3: Second off Chiralcel AD[®] column; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.17-7.33 (m, 5 H), 4.54 (s, 2 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.14-3.02 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.64-1.84 (m, 4 H).

5 **Example 6 - Preparation of Compound VI**

A one-necked, 10-mL, round-bottomed flask equipped with a rubber septum and an argon needle inlet was charged with 0.5 mL of pyridine, Example 1 (0.0070 g, 0.014 mmol), and acetic anhydride (0.020 mL, 22 mg, 0.21 mmol). The reaction mixture was stirred for 2 h at room temperature, and then added to 30 mL of 1N HCl. The resulting mixture was extracted with three 10 30 mL portions of ethyl acetate, the combined organic phases were dried over MgSO₄ and concentrated. Purification via HPLC (2.5% ethyl acetate-dichloromethane with 0.01% trifluoroacetic acid) afforded 3 mg (38%) of Example 6. MP 137 °C.

Example 7 - Preparation of Compound VII

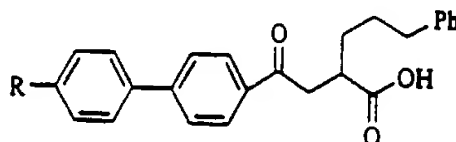
15 A one-necked, 15-mL, round-bottomed flask equipped with a rubber septum and an argon needle inlet was charged with 2 mL of triethylamine, 2 mL of THF, compound I (0.0570 g, 0.134 mmol), and ethyl chloroformate (0.032 mL, 36 mg, 0.34 mmol). The reaction mixture was stirred for 16 h at room temperature and then added to 50 mL of 1N HCl. The resulting mixture was extracted with three 50 mL portions of ethyl acetate, the combined organic phases were dried over 20 MgSO₄ and concentrated. Column chromatography on 10 g silica gel (40% ethyl acetate-hexanes with 0.5% HOAc) followed by purification via HPLC (1.5% ethyl acetate-dichloromethane with 0.01% trifluoroacetic acid) afforded 1 mg (1.5%) of Example 7. MS (FAB-LSIMS) 499 [M+H]⁺.

Example 11 - Preparation of Compound XI

A one-necked, 25-mL, round-bottomed flask equipped with a rubber septum and an argon needle inlet was charged with 1 mL of CH_2Cl_2 , Example 12 (0.012 g, 0.026 mmol), and the Dess-Martin reagent (16 mg, 0.038 mmol) prepared according to Dess, et al., J. Org. Chem. 48, 4156, 1983. The resulting mixture was stirred for 30 min at 0 °C, diluted with 30 mL of ethyl acetate, and washed with two 20 mL portions of 1N HCl. The organic layer was dried over MgSO_4 and concentrated. Purification via HPLC (1.5% ethyl acetate-dichloromethane with 0.01% trifluoroacetic acid) afforded 1 mg (9%) of Example 11. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.70 (t, J = 1.3 Hz, 1 H), 8.05 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.15-7.35 (m, 5 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.14-3.02 (m, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 2.48 (t, J = 7.5 Hz, 2 H), 2.41 (dt, J = 1.3 Hz and 6.3 Hz, 2 H), 1.96 (m, 2 H), 1.64-1.84 (m, 4 H).

The above methods for the preparation of Example 1, Example 2, Example 6, Example 7, and Example 11 were used to prepare the following series of biphenyl containing products.

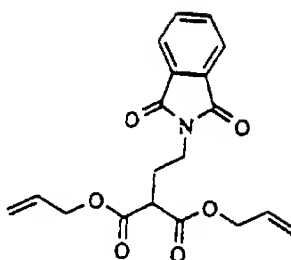
TABLE I



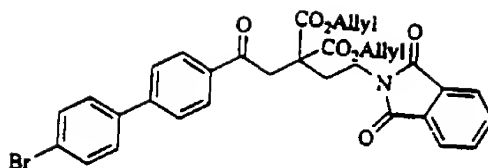
comp	R	isomer	m.p.(°C)/other characterization
I	HOCH ₂ C≡C	R,S	130
II	HOCH ₂ C≡C	S	¹ H NMR (300 MHz, CDCl ₃) δ 8.02 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.17-7.33 (m, 5 H), 4.54 (s, 2 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.02-3.14 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.64-1.84 (m, 4 H).
III	HOCH ₂ C≡C	R	¹ H NMR (300 MHz, CDCl ₃) δ 8.02 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.17-7.33 (m, 5 H), 4.54 (s, 2 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.02-3.14 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.64-1.84 (m, 4 H).
IV	MeOCH ₂ C≡C	R,S	136
V	(n-Pr) ₂ NCH ₂ C≡C	R,S	MS (FAB-LSIMS) 510 [M+H] ⁺
VI	CH ₃ CO ₂ CH ₂ C≡C	R,S	137
VII	EtOCO ₂ CH ₂ C≡C	R,S	MS (FAB-LSIMS) 499 [M+H] ⁺
VIII	HO(CH ₂) ₂ C≡C	R,S	124
IX	CH ₃ CO ₂ (CH ₂) ₂ C≡C	R,S	MS (FAB-LSIMS) 483 [M+H] ⁺
X	HO ₂ C(CH ₂) ₂ C≡C	R,S	184
XI	OHC(CH ₂) ₂ C≡C	R,S	¹ H NMR (300 MHz, CDCl ₃) δ 9.70 (t, J = 1.3 Hz, 1 H), 8.05 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.15-7.35 (m, 5 H), 3.46 (dd, J = 8.1, 16.8 Hz, 1 H), 3.14-3.02 (m, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 2.48 (t, J = 7.5 Hz, 2 H), 2.41 (dt, J = 1.3 Hz and 6.3 Hz, 2 H), 1.96 (m, 2 H), 1.64-1.84 (m, 4 H).

XII	$\text{HO}(\text{CH}_2)_4\text{C}\equiv\text{C}$	R,S	123
XIII	$\text{PhC}\equiv\text{C}$	R,S	154
XIV	3-HO- $\text{PhC}\equiv\text{C}$	R,S	237

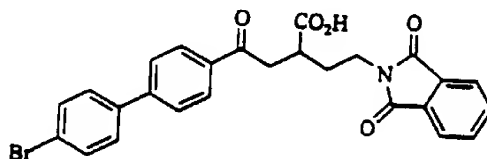
5 Example 15 - Preparation of Compound XV



15 **Step 1** A solution of sodium hydride (4.35 g, 181 mmol) in freshly distilled THF (100 mL) was cooled to 0 °C and treated with commercially available diallyl malonate (35.0 g, 190 mmol) over 40 min via a dropping funnel. After stirring at room temperature for 30 min, N-(2-bromoethyl)phthalimide (43.9 g, 247 mmol) was added to the solution in one portion and the mixture was heated to reflux. After 48 h the solution was cooled to 0 °C, quenched with 2N HCl and concentrated to about 20% of its original volume. The concentrate was diluted with ethyl acetate (300 mL) and washed successively with saturated aqueous solutions of K_2CO_3 and NaCl. The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (gradient elution with 5-25% ethyl acetate-hexanes) 20 afforded diallyl 2-phthalimidoethylmalonate (41.2 g, 64%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.82 (m, 2H), 7.72 (m, 2H), 5.85 (m, 2H), 5.30 (m, 2H), 5.22 (m, 2H), 4.60 (m, 4H), 3.80 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 7.2 Hz, 1H), 2.30 (dd, J = 13.8, 6.9 Hz, 2H).

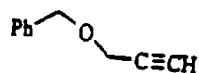


5 **Step 2** A solution of the product of step 1 (5.20 g, 14.6 mmol) in freshly distilled THF (100 mL) was cooled to 0 °C, while NaH (385 mg, 16.1 mmol) was slowly added. After 40 minutes, the reaction mixture was warmed to room temperature, the product of Example 1, step 2 (4.55 g, 14.6 mmol) was added in portions, and the mixture was stirred for 24 h. The reaction mixture was cooled to 0 °C, quenched slowly with 2N HCl (300 mL), extracted with one 150 mL portion of
 10 dichloromethane and two 100 mL portions of dichloromethane. The combined organic phases were dried over MgSO₄, filtered and concentrated to afford 6.50 g (71%) of the desired product which was used in step 3 without purification. TLC (30% ethyl acetate-hexanes): R_f = 0.4.

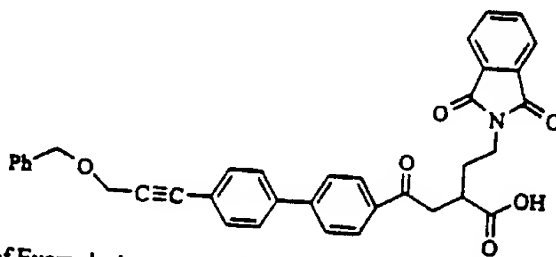


15 **Step 3** A solution of the product of step 2 (6.50 g, 10.4 mmol) in 1,4-dioxane (100 mL) was cooled to 0 °C, while tetrakis(triphenylphosphine)palladium (0.180 g, 146 mmol) and pyrrolidine (2.40 mL, 29.2 mmol) were added sequentially. After stirring for 2 h at 0 °C and 4 h at room temperature, the
 20 reaction mixture was poured into 2N HCl (100 mL). The resulting mixture was extracted with four 100 mL portions of dichloromethane, the combined organic phases were dried over MgSO₄, and concentrated to give the diacid as a yellow solid (9.70 g). A 3.8 g sample of this material was dissolved in 1,4-dioxane (150 mL) and heated at reflux for 1 h. After cooling to room temperature,

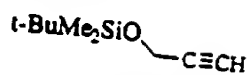
the solution was concentrated and the residue was chromatographed on 300 g silica gel (gradient with 5%-15% methanol-dichloromethane) to give the desired acid (0.300 g) which was further purified via recrystallization to afford 0.170 g (59% overall yield from step 2) of the desired product as a white crystalline solid. MP 209-210 °C.



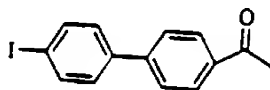
Step 4 A one-necked, 100-mL. round-bottomed flask equipped with a rubber septum and an argon needle inlet containing 2 ml of THF was charged with NaH (435 mg, 17.2 mmol) and cooled to 0 °C while propargyl alcohol (1.0 mL, 0.963 g, 17.2 mmol) was added via syringe over ca. 5 min. The resulting mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. Benzylbromide (1.8 mL, 2.59 g, 15.1 mmol) was added, the reaction mixture was stirred at room temperature for 36 h, poured into pentane (150 mL), and washed with a 100 mL portion of brine. The solvent was removed via distillation and the residue (3.5 g of a yellow oil) was used in step 5 directly. ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.31 (m, 5 H), 4.61 (s, 2H), 4.17 (d, *J*=2.4 Hz, 2 H), 2.47 (t, *J*= 2.4 Hz, 1 H).



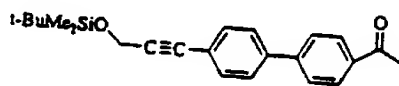
Step 5 The procedure of Example 1, step 5 was used to prepare Example 15 using the product from step 4 and the product of step 3 as starting materials. MP 151 °C.

Example 16 - Preparation of Compound XVI

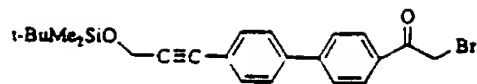
Step 1 A one-necked, 100-mL, round-bottomed flask equipped with a rubber septum and an argon
 needle inlet was charged with propargyl alcohol (1.0 mL, 0.963 g, 17.2 mmol), ether (20 ml), and
 cooled to 0 °C while NaH (435 mg, 17.2 mmol) was added slowly. The resulting mixture was
 stirred at room temperature for 1 h, and *t*-butyldimethylsilyl chloride (2.60 g, 17.2 mmol) was added.
 The reaction mixture was stirred at room temperature for 6 h, poured into hexane (150 mL), and
 washed with 1 N HCl. The organic phase was dried over MgSO₄ and concentrated to afford 2.88
 g of a yellow oil which was used in step 2 without purification. ¹H NMR (300 MHz, CDCl₃) δ 4.29
 (d, *J* = 2.1 Hz, 2 H), 2.37 (t, *J* = 2.1 Hz, 1 H), 0.89 (s, 9 H), 0.11 (s, 3 H).



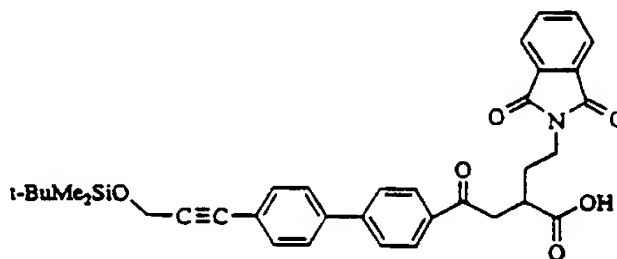
Step 2 The procedure of Example 1, step 2 was used to prepare the desired acetyl biphenyl using
 commercially available 4-iodobiphenyl and acetyl chloride. TLC (10% ethyl acetate-hexanes): *R_f* =
 0.3.



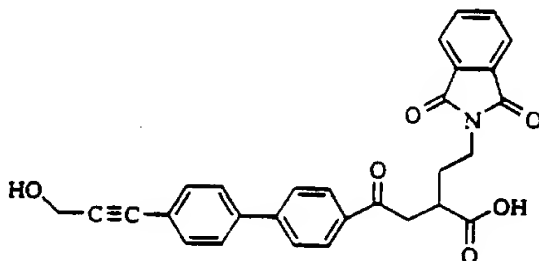
Step 3 The procedure of Example 1, step 5 was used to prepare the desired biphenyl acetylene using
 the product of step 1 and the product of step 2. TLC (10% ethyl acetate-hexanes): *R_f* = 0.4.



Step 4 A one-necked, 50-mL, round-bottomed flask equipped with a rubber septum and an argon
5 needle inlet was charged with 5 mL of THF, the product of step 3 (1.06 g, 2.94 mmol), and cooled
to -78 °C while potassium hexamethyldisilazide (617 mg, 2.94 mmol) was added dropwise via
syringe. The reaction mixture was stirred at -78 °C for 30 min, trimethylsilyl chloride (0.374 mL,
0.320 g, 2.94 mmol) was added dropwise via syringe, and the resulting mixture was stirred at -78
°C for 3 h. The reaction mixture was warmed to 0 °C for 1 h. *N*-bromosuccinimide (0.540 g, 2.94
10 mmol) was added, and the mixture was allowed to warm to room temperature and stirred 16 h. The
reaction mixture was poured into a 100 mL portion of aqueous saturated NH_4Cl , and extracted with
three 50 mL portions of dichloromethane. The combined organic phases were dried over MgSO_4
and concentrated. Column chromatography on 200 g of silica gel (gradient elution with 0- 5% ethyl
acetate-hexanes) afforded 0.264 g (20%) of the bromomethyl ketone. TLC (10% ethyl
15 acetate-hexanes): R_f 0.5.



Step 5 The procedures of Example 15, steps 2-3 were used to prepare the desired biphenyl phthalimide using the product of step 4. TLC (50% ethyl acetate-hexanes with 1% acetic acid): R_f = 0.3.



Step 6 A one-necked, 50-mL, round-bottomed flask equipped with a rubber septum and an argon needle inlet was charged with 10 mL of CH₂Cl₂, the product from step 5 (0.040 g, 0.067 mmol), and 2 mL of HF-pyridine. The resulting mixture was stirred for 10 minutes at room temperature, diluted with a 75 mL portion of water, and extracted with a 75 mL portion of CH₂Cl₂. The organic phase was dried over MgSO₄ and concentrated. Column chromatography on 5 g of silica gel (25% ethyl acetate-hexanes with 1% HOAc) afforded 6 mg (19%) of Example 16. MP 145 °C.

Example 17

Biological Assays of Invention Compounds

P218 Quenched Fluorescence Assay for MMP Inhibition:

The P218 quenched fluorescence assay (Microfluorometric Profiling Assay) is a modification of that originally described by Knight, et al., FEBS Lett. 296, 263, 1992 for a related substance and a variety of matrix metalloproteinases (MMPs) in cuvettes. The assay was run with each invention compound and the three MMPs, Mmp-3, MMP-9 and MMP-2, analyzed in parallel, adapted as follows for a 96-well microtiter plate and a Hamilton AT® workstation.

P218 Fluorogenic Substrate: P218 is a synthetic substrate containing a 4-acetyl-7-methoxycoumarin (MCA) group in the N-terminal position and a 3-[2, 4-dinitrophenyl]-L-2,3-diaminopropionyl (DPA) group internally. This is a modification of a peptide reported by Knight (1992) that was used as a substrate for matrix metalloproteinases. Once the P218 peptide is cleaved (putative clip site at the Ala-Leu bond), the fluorescence of the MCA group can be detected on a fluorometer with excitation at 328 nm and emission at 393 nm. P218 is currently being produced BACHEM exclusively for Bayer. P218 has the structure:

H-MCA-Pro-Lys-Pro-Leu-Ala-Leu-DPA-Ala-Arg-NH₂ (MW 1332.2)

Recombinant Human CHO Stromelysin (MMP-3)

Recombinant Human CHO Pro-MMP-3: Human CHO pro-stromelysin-257 (pro-MMP-3) was expressed and purified as described by Housley, et al., J. Biol. Chem. 268, 4481, 1993.

Activation of Pro-MMP-3: Pro-MMP-3 at 1.72 μ M (100 μ g/mL) in 5 mM Tris at pH 7.5, 5 mM CaCl₂, 25 mM NaCl, and 0.005% Brij-35 (MMP-3) activation buffer) was activated by incubation with TPCK (N-tosyl-(L)-phenylalanine chloromethyl ketone) trypsin (1:100 w/w to pro-MMP-3) at 25 °C for 30 min. The reaction was stopped by addition of soybean trypsin inhibitor (SBTI; 5:1 w/w to trypsin concentration). This activation protocol results in the formation of 45 kDa active MMP-3, which still contains the C-terminal portion of the enzyme.

Preparation of Human Recombinant Pro-Gelatinase A (MMP-2):

Recombinant Human Pro-MMP-2: Human pro-gelatinase A (pro-MMP-2) was prepared using a vaccinia expression system according to the method of Fridman, et al., J. Biol. Chem. 267, 15398, 1992.

Activation of Pro-MMP-2: Pro-MMP-2 at 252 mg/mL was diluted 1:5 to a final concentration of 50 µg/mL solution in 25 mM Tris at pH 7.5, 5 mM CaCl₂, 150 mM NaCl, and 0.005% Brij-35 (MMP-2 activation buffer). *p*-Aminophenylmercuric acetate (APMA) was prepared in 10 mM (3.5 mg/mL) in 0.05 NaOH. The APMA solution was added at 1:20 the reaction volume for a final APMA concentration of 0.5 mM, and the enzyme was incubated at 37 °C for 30 min. Activated MMP-2 (15 mL) was dialyzed twice vs. 2 L of MMP-2 activation buffer (dialysis membranes were pre-treated with a solution consisting of 0.1% BSA in MMP-2 activation buffer for 1 min. followed by extensive H₂O washing). The enzyme was concentrated on Centricon concentrators (concentrators were also pre-treated a solution consisting of 0.1% BSA in MMP-2 activation buffer for 1 min., followed by washing with H₂O, then MMP-2 activation buffer) with re-dilution followed by re-concentration repeated twice. The enzyme was diluted to 7.5 mL (0.5 times the original volume) with MMP-2 activation buffer.

Preparation of Human Recombinant Pro-Gelatinase B (MMP-9):

Recombinant Human Pro-MMP-9: Human pro-gelatinase B (pro-MMP-9) derived from U937 cDNA as described by Wilhelm, et al. J. Biol. Chem. 264, 17213, 1989 was expressed as the full-length form using a baculovirus protein expression system. The pro-enzyme was purified using methods previously described by Hibbs, et al. J. Biol. Chem. 260, 2493, 1984.

Activation of Pro-MMP-9: Pro-MMP-9 20 µg/mL in 50 mM Tris at pH 7.4, 10mM CaCl₂, 150 mM NaCl, and 0.005% Brij-35 (MMP-9 activation buffer) was activated by incubation with 0.5 mM *p*-aminophenylmercuric acetate (APMA) for 3.5 h at 37 °C. The enzyme was dialyzed against the same buffer to remove the APMA.

Instrumentation:

Hamilton Microlab AT Plus: The MMP-Profiling Assay is performed robotically on a Hamilton MicroLab AT Plus[®]. The Hamilton is programmed to: (1) serially dilute up to 11 potential inhibitors automatically from a 2.5 mM stock in 100% DMSO; (2) distribute substrate followed by inhibitor into a 96 well Cytofluor plate; and (3) add a single enzyme to the plate with mixing to start the reaction. Subsequent plates for each additional enzyme are prepared automatically by beginning the program at the substrate addition point, remixing the diluted inhibitors and beginning the reaction by addition of enzyme. In this way, all MMP assays were done using the same inhibitor dilutions.

Millipore Cytofluor II. Following incubation, the plate was read on a Cytofluor II fluorometric plate reader with excitation at 340 nM and emission at 395 nM with the gain set at 80.

Buffers:

Microfluorometric Reaction Buffer (MRB): Dilution of test compounds, enzymes, and P218 substrate for the microfluorometric assay were made in microfluorometric reaction buffer consisting of 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) at pH 6.5 with 10 mM CaCl₂, 150 mM NaCl, 0.005% Brij-35 and 1% DMSO.

Methods:

MMP Microfluorometric Profiling Assay. The assay is done with a final substrate concentration of 6 μ M P218 and approximately .5 to .8 nM MMP with variable drug concentrations. The Hamilton is programmed to serially dilute up to 11 compounds from a 2.5 mM stock (100% DMSO) to 10x the final compounds concentrations in the assay. Initially, the instrument delivers various amounts of microfluorometric reaction buffer (MRB) to a 96 tube rack of 1 ml Marsh

dilution tubes. The instrument then picks up 20 μ l of inhibitor (2.5 mM) from the sample rack and mixes it with a buffer in row A of the Marsh rack, resulting in a 50 μ M drug concentration. The inhibitors are then serially diluted to 10, 5, 1, .2, .05 and .01 μ M. Position 1 on the sample rack contains only DMSO for the "enzyme-only" wells in the assay, which results in no inhibitor in column 1, rows A through H. The instrument then distributes 107 μ l of P218 substrate (8.2 μ M in MRB) to a single 96 well cytofluor microtiter plate. The instrument re-mixes and loads 14.5 μ l of diluted compound from rows A to G in the Marsh rack to corresponding rows in the microtiter plate. (Row H represents the "background" row and 39.5 μ l of MRB is delivered in placed of drug or enzyme). The reaction is started by adding 25 μ l of the appropriate enzyme (at 5.86 times the final enzyme concentration) from a BSA treated reagent reservoir to each well, excluding Row H, the "background" row. (The enzyme reservoir is pretreated with 1% BSA in 50 mM Tris, pH 7.5 containing 150 mM NaCl for 1 hour at room temp., followed by extensive H₂O washing and drying at room temp.).

After addition and mixing of the enzyme, the plate is covered and incubated for 25 min. at 37 °C. Additional enzymes are tested in the same manner by beginning the Hamilton program with the distribution of P218 substrate to the microtiter plate, followed by re-mixing and distribution of the drug from the same Marsh rack to the microtiter plate. The second (or third, etc.) MMP to be tested is then distributed from a reagent rack to the microtiter plate with mixing, prior to covering and incubation. This is repeated for all additional MMP's to be tested.

IC50 Determination in Microfluorometric Assay: Data generated on the Cytofluor II is copied from an exported ".CSV" file to a master Excel spreadsheet. Data from several different MMPs (one 96 well plate per MMP) were calculated simultaneously. The percent inhibition is

determination for each drug concentration by comparing the amount of hydrolysis (fluorescence units generated over 25 minutes of hydrolysis) of wells containing compound with the "enzyme only" wells in column 1. Following subtraction of the background the percent inhibition was calculated as:

$$((\text{Control values} - \text{Treated values}) / \text{Control values}) \times 100$$

Percent inhibitions were determined for inhibitor concentrations of 5, 1, 0.5, 0.1, 0.02, 0.005 and 0.001 μM of drug. Linear regression analysis of percent inhibition versus log inhibitor concentration was used to obtain IC_{50} values.

Table II

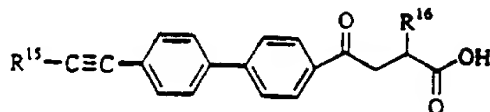
COMP.#	MMP-3 Fluorogenic IC-50	MMP-9 Fluorogenic IC-50	MMP-2 Fluorogenic IC-50
I	21	106	4
II	2184	I = 35%	252
III	5	37	1
IV	38	704	21
V	327	2630	235
VI	36	834	14
VII	67	2460	103
VIII	32	122	6
IX	57	542	37
X	203	I = 27%	108
XI	1730	I = 24%	596
XII	56.6	614	36
XIII	405		245

XIV	125	$I = 46\%$	85
XV	11	40	5
XVI	4	2	1

- 5 Other embodiments of the invention will be apparent to those skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

We claim:

1. Matrix metalloproteinase inhibiting compounds having the general formula:

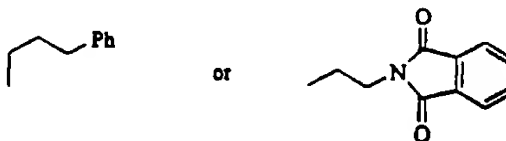


5 wherein

R^{15} is selected from the group comprising: HOCH_2 , MeOCH_2 , $(n\text{-Pr})_2\text{NCH}_2$, $\text{CH}_3\text{CO}_2\text{CH}_2$, $\text{EtOCO}_2\text{CH}_2$, $\text{HO}(\text{CH}_2)_2$, $\text{CH}_3\text{CO}_2(\text{CH}_2)_2$, $\text{HO}_2\text{C}(\text{CH}_2)_2$, $\text{OHC}(\text{CH}_2)_2$, $\text{HO}(\text{CH}_2)_4$, Ph, 3-HO-Ph. and $\text{PhCH}_2\text{OCH}_2$; and

R^{16} is selected from:

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2. A composition having matrix metalloproteinase inhibitory activity, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

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3. A method of inhibiting matrix metalloproteinase activity in a mammal comprising administration of an effective amount of the matrix metalloproteinase inhibitor compound of claim 1 to said mammal.

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4. The method of claim 3 wherein said mammal is a human.

5. A method of treating a mammal comprising administering to the mammal a matrix metalloproteinase inhibiting amount of a compound according to claim 1 sufficient to:

(a) alleviate the effects of osteoarthritis, rheumatoid arthritis, septic arthritis, periodontal disease, corneal ulceration, proteinuria, aneurysmal aortic disease, dystrophic epidermolysis, bullosa, conditions leading to inflammatory responses, osteopenias mediated by MMP activity, temporomandibular joint disease, demyelating diseases of the nervous system;

(b) retard tumor metastasis or degenerative cartilage loss following traumatic joint injury;

(c) reduce coronary thrombosis from atherosclerotic plaque rupture; or

(d) effect birth control.

- 10 6. The method of claim 5 wherein the effect is alleviation of osteoarthritis.
7. The method of claim 5 wherein the effect is retardation of tumor metastasis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 97/07921

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/34 A61K31/19 C07D209/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 3 784 701 A (TOMCUFCIK A ET AL) 8 January 1974 see claims ---	1-7
A	CHILD, R. G. ET AL: "A new nonsteroidal antiinflammatory analgesic: gamma.-oxo(1,1'- biphenyl)-4-butanoic acid (Fenbufen). Chemistry and activity of analogs" ARZNEIM.-FORSCH. (1980), 30(4A), 695-702 CODEN: ARZNAD;ISSN: 0004-4172, 1980, XP002043280 ---	1-7
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

15 October 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07921

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	--- CHILD, RALPH G. ET AL: "Fenbufen, a new anti-inflammatory analgesic: synthesis and structure-activity relations of analogs" J. PHARM. SCI. (1977), 66(4), 466-76 CODEN: JPMSAE, 1977, XP000560277	1-7
P,X	--- WO 96 15096 A (BAYER AG ;KLUENDER HAROLD CLINTON EUGENE (US); BENZ GUENTER H H H) 23 May 1996 see page 164; claims -----	1-7

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